UK National Screening Committee

# Screening for Metachromatic Leukodystrophy

## An evidence map to outline the volume and type of evidence related to screening for metachromatic leukodystrophy for the UK National Screening Committee

Version: 1.2

Author: Costello Medical

Date: June 2023

**The UK National Screening Committee secretariat is hosted by the Department of Health and Social Care**

# Contents

# About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.

Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

UK National Screening Committee, Southside, 39 Victoria Street, London, SW1H 0EU

www.gov.uk/uknsc

Blog: https://nationalscreening.blog.gov.uk/

For queries relating to this document, please contact: https://view-health-screening-recommendations.service.gov.uk/helpdesk/

# Summary

This document discusses the findings of the evidence map on screening for metachromatic leukodystrophy (MLD).

Evidence maps are a way of scanning published literature to look at the volume and type of evidence in relation to a specific topic. They inform whether the evidence is sufficient to commission a more sustained analysis on the topic under consideration. In particular, this evidence map aims to assess the volume and type of evidence published on the treatment of MLD and its outcomes, as well as the performance of newborn screening for MLD through a 2-tiered approach using dried blood spots, and the cost-effectiveness of treatment or screening for MLD. This evidence map will support a wider discussion on whether the UK NSC should commission further work on this topic.

Based on the findings of this evidence map, there is sufficient published literature, particularly in relation to the treatment, to justify further work on screening for MLD. The available evidence on test accuracy and cost-effectiveness, though limited, is promising and warrants further review. Given that screening for MLD has not been previously considered by the UK National Screening Committee (UK NSC), it is also recommended that the topic should be added to the UK NSC recommendations list.

# Introduction and approach

## Background and objectives

The UK National Screening Committee (UK NSC) external reviews (also known as evidence summaries or evidence reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

The UK NSC has not previously considered screening for metachromatic leukodystrophy (MLD).

The proposal for screening for MLD was submitted to the UK NSC during the 2021 annual call for topics. The proposal suggests screening newborns for MLD as part of the existing newborn blood spot screening programme via a 2-tier test strategy utilising routine dried blood spots (DBS) and existing tandem mass spectrometry (MS/MS) technology followed by genetic confirmatory testing.

The UK NSC agreed that work should be undertaken to consider the topic of screening for MLD in the form of an evidence map.

## Description of the condition

Metachromatic leukodystrophy (MLD), also known as Arylsulfatase A deficiency or ARSA deficiency, is an autosomal recessive hereditary neurodegenerative disease belonging to the family of lysosomal storage diseases.[1, 2] Deficiency in the ARSA enzyme leads to accumulation of sulfatides, causing damage to the myelin sheath that insulates the neurons of the central and peripheral nervous systems. This damage manifests in progressive motor and cognitive impairment.[1, 2] The incidence of MLD in the UK is estimated at approximately 1 in 40,000 births.[3]

There are 3 different forms of MLD, classified according to the age at which symptoms first appear. The late infantile form has the earliest age of onset, typically presenting before 30 months of age, and is the most common type of MLD, affecting 50-60% of individuals.[1, 2] Rapid progression of the late infantile form usually leads to death before age 5.[4] The juvenile form typically presents between 3 and 16 years of age, affecting approximately 20-35% of children with MLD, with survival usually less than 20 years.[5, 6] The adult form of MLD is least common with slower progression, usually presenting after 16 years, with periods of stability and progression occurring until death, typically between 6 to 14 years of diagnosis.[1, 4] Specific symptoms of MLD can vary by form. Infants with late-infantile MLD usually first present with muscle weakness, clumsiness, frequent falling, toe walking and dysarthria, later progressing to delays or regression or cognitive

and motor skills, as well as pain, seizures, hearing and vision loss, eventually leading to general unawareness of surroundings.[1] Children with the juvenile form of MLD often present with a decline in school performance or behavioural problems, while onset of MLD in adults can be first characterised by changes in school or job performance, along with emotional problems, psychosis, and neurological symptoms.[1]

Diagnosis of MLD can be informed by measurement of sulfatides in the blood or urine, measurement of ARSA enzymatic activity in the blood, and magnetic resonance imaging (MRI) brain scans, with genetic sequencing for mutations in the ARSA gene regarded as the most accurate method and therefore often used as the confirmatory test.[2, 3] Low ARSA enzymatic activity alone is not considered sufficient to diagnose MLD. This is due to the relatively high prevalence of the ARSA pseudodeficiency allele, which leads to enzymatic activity of 5 to 20% of normal controls[1]. However, this pseudodeficiency is not known to manifest as disease or as neurological symptoms[7]. Secondary tests such as measurement of sulfatides and/or genetic confirmatory testing are therefore recommended to rule out other rare demyelinating disorders with coincidental ARSA pseudodeficiency.[8]

MLD is usually detected after birth, once clinical symptoms have manifested, unless the parents are aware that they carry the mutation based on family history, or development of MLD in previous children.[5] As MLD is an autosomal recessive disease, a sibling of an affected individual has a 25% chance of developing the disease, and a 50% chance of being an asymptomatic carrier in the case of heterozygosity.[1] Without prenatal or newborn screening, or any prior knowledge of genetic risk for MLD, early diagnosis is challenging, subsequently restricting the potential window for optimal treatment.[5]

## Current treatments

Treatments investigated for MLD have included bone marrow or haematopoietic stem cell transplantation (HSCT), enzyme replacement therapy, cell therapies and gene therapies.[8, 9] Bone marrow or HSCT was initially anticipated to be a viable treatment option for MLD, but has been acknowledged to have significant limitations and poor efficacy,[8] particularly once disease has presented and started to progress.[10] Best supportive care has been the main treatment for management of symptoms, particularly for children with the late infantile form for whom disease management has primarily focused on palliative care, demonstrating unmet need for effective treatments.[5, 11]

In 2022, Atidarsagene autotemcel (ARSA-cel/OTL-200, developed by Orchard Therapeutics and branded as Libmeldy) was recommended by the National Institute for Health and Care Excellence (NICE) as an option for treating MLD in either presymptomatic children with late infantile or early juvenile MLD, as well as in children with early juvenile MLD with early clinical signs or symptoms (who can still walk independently with no cognitive decline) (HST18).[5] Libmeldy is an autologous haematopoietic stem cell gene therapy (H

SC-GT), which involves removing and correcting a patient's stem cells by inserting a functional copy of the ARSA gene, before returning the cells to the patient.[11] The HST18 submission was supported by clinical evidence from 2 non-randomised, prospective single-centre studies of Libmeldy in children with late infantile or early juvenile forms of MLD, along with data from 3 expanded access programmes (EAP) and inputs from patient and clinical experts. One of the clinical studies, TIGET-MLD trial (NCT01560182) initiated in 2010 in Italy, was identified in this evidence map (see Appendix 2 for abstracts reporting on this study). The second clinical study was initiated in 2018, also in Italy, with 8 years of follow-up planned (NCT03392987). At the time of the HST18 submission, the primary endpoint of change from baseline in Gross Motor Function Measure (GMFM) score at 24 months post-treatment had not yet been reached for any patients, therefore unpublished preliminary data from 4 patients was evaluated. [5]

While the long-term benefits are still uncertain, the available clinical data from the 2 studies and EAPs supported that Libmeldy could correct ARSA deficiency with a sustained clinical benefit on the mobility and cognitive function in MLD compared with the natural history cohort, and was tolerated well. Cost-effectiveness estimates were within what NICE considers as acceptable use of National Health Service (NHS) resources for highly specialised technologies, due to the substantial benefit in clinical health outcomes and quality-of-life.[5]

It is stated that Libmeldy should be delivered in a highly specialised service by a specialist multidisciplinary team.[5] In Europe, there are currently 5 centres that are able to offer the treatment, with the first baby in the UK treated with Libmeldy on the NHS at the Royal Manchester Children's Hospital (in collaboration with the Manchester Centre for Genomic Medicine) in August 2022.[12]

Routine screening for MLD in newborns is not currently performed in the UK. Screening was discussed as part of the NICE HST18 appraisal; with clinical and patient experts emphasising the importance of early diagnosis and newborn screening for inherited disorders such as MLD, with the NICE committee acknowledging the difficulties of diagnosis without knowledge of an affected sibling.[5]

## Proposal for screening for MLD: supporting publications

The annual call proposal for screening for MLD included 10 publications in support of the submission.[1, 8, 13-20] Of these, 2 studies investigated treatments for MLD.[8, 19] One reported long-term outcomes following allogeneic HSCT[8] and another was an phase I/II non-RCT investigating Libmeldy.[19] The latter study was identified in this evidence map and is discussed below. Three studies reported on the natural history of MLD, 2 of which were cohort studies,[17, 18] with the other reporting results from caregiver interviews.[14]

Strategies for MLD screening were described in 4 studies in the annual call proposal.[13, 15, 16, 20] Two of these studies assessed sulfatide analysis and ARSA activity individually,[16, 20] whilst another combined these tests, investigating them as a 2-tier screening strategy in over 27,000 D B S samples.[15] As the study assessing the 2-tier strategy was identified as a relevant study in this evidence map, it is discussed below. Another study included in the annual call submission, and in this evidence map, was a cost-utility analysis which found that newborn screening for MLD is a cost-effective use of NHS resources.[13] The remaining publication was a narrative review that described various aspects of MLD, including natural history, diagnosis and management.[1]

In addition, the annual call submission cited 2 prospective pilot studies that are ongoing in Northern Germany and the U S state of New York. These pilot studies plan to assess multi-tier screening approaches for MLD.[21, 22] Based on an article published in 2021, the planned duration of the study in Northern Germany is 12 months, with an extension of 1 or 2 years.[21, 22] The New York-based study expects to enrol individuals over a 5-year period.[21, 22]

## Aims of the evidence map

Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic.

This evidence map has been developed to assess whether a more sustained review on screening for MLD should be commissioned in 2023 and to evaluate the volume and type of evidence on key issues related to screening for MLD.

The aim was to address the following questions:

1. What is the volume and type of evidence on the accuracy of newborn screening strategies for MLD using dried blood spots?
2. What is the volume and type of evidence available on the benefits and/or harms of interventions in presymptomatic/asymptomatic children with MLD identified through screening? I.e. does early initiation of treatment following screening provide better outcomes for MLD compared with initiation of treatment following clinical detection?
3. What is the volume and type of evidence on the cost-effectiveness of treatment or screening for MLD in asymptomatic or symptomatic patients?

The objective, therefore, is to assess the volume and type of evidence relevant to screening for MLD, with a focus on the treatment of MLD and its outcomes, as well as the cost-effectiveness of treatment or screening and the performance of newborn screening for MLD through a 2-tiered approach using DBS.

The findings of this evidence map will provide the basis for discussion to support decision making on whether there is sufficient evidence to justify commissioning a more sustained review of the evidence on MLD in 2023. The aim of this document is to present the information necessary for the UK NSC to decide this.

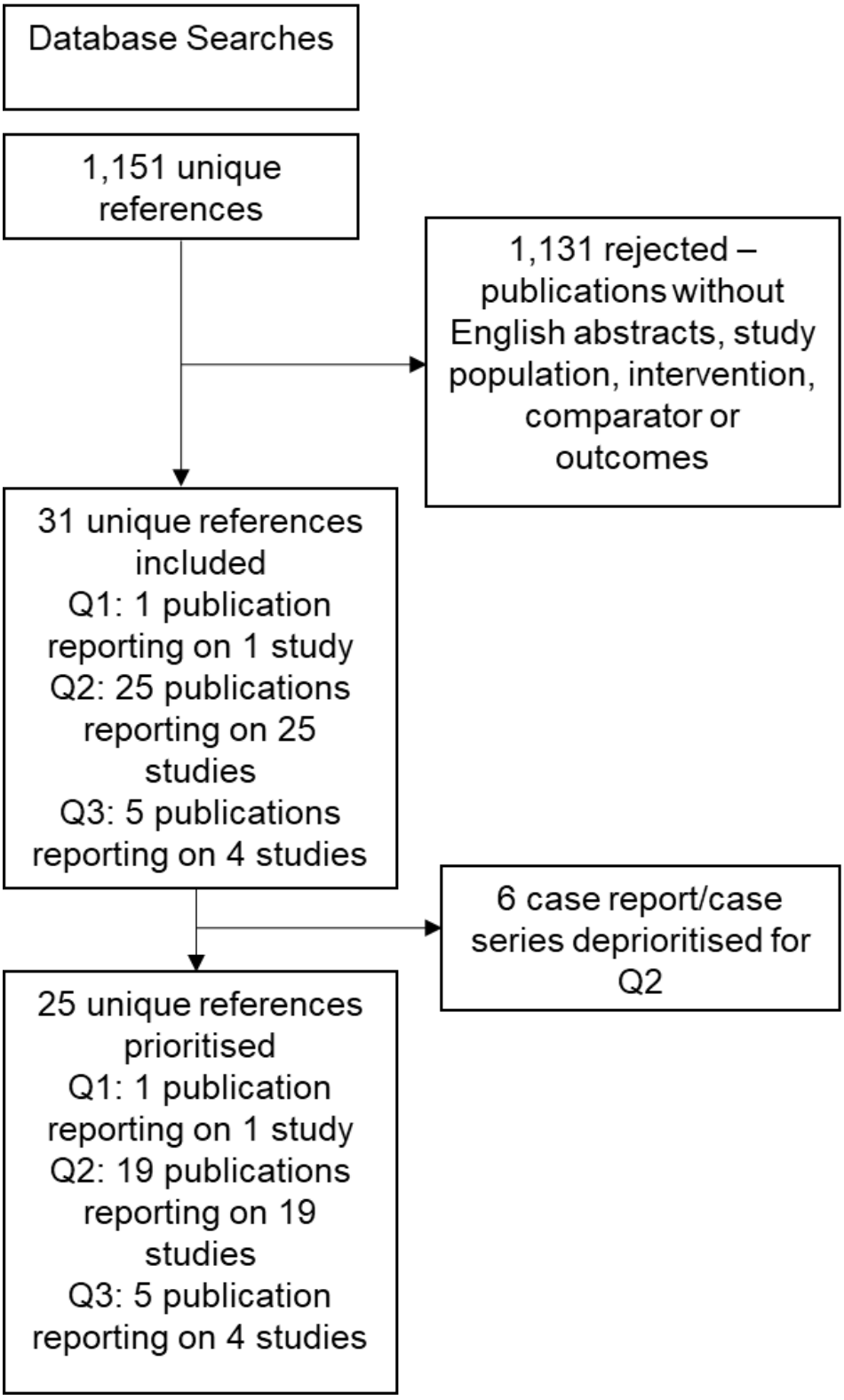
# Search methods and results

The searches were conducted on 24th April 2023 in the following databases: MEDLINE, Embase, the Cochrane Libraries, National Health System Economic Evaluation Database (NHS-EED) and Health Technology Assessment (HTA) database. The search period was restricted from 1 January 2012 to the date of the searches. The detailed search strategies, including exclusion and inclusion criteria are available in Appendix 1.

One reviewer screened all titles and abstracts with a second reviewer checking all included and 10% of excluded decisions. All references were reviewed at abstract level, though in some cases full-texts were reviewed to clarify uncertain pieces of information. A formal quality appraisal of the evidence was not required, given the remit of the evidence map. Abstract reporting information is available in Appendix 2.

The search returned 1,163 results. After automatic and manual de-duplication, 1,151 unique references were reviewed for relevance to the review questions. Thirty-one records were included in the evidence map; 1 presented relevant results for question 1, 25 for question 2 and 5 (reporting on 4 studies) for question 3. A flow diagram summarising the number of studies included and excluded is presented in Figure 1.

**Figure 1: Summary of included and excluded publications**



# Summary of findings

## Question 1: What is the volume and type of evidence on the accuracy of newborn screening strategies for MLD using dried blood spots?

Of the 1,151 abstracts reviewed, 1 study was included for this question.[15]

Hong 2021, a publication included in the annual call proposal, was a cohort study that evaluated a 2-tiered screening algorithm, designed to minimise the risk of false-positive results.[15] The primary screening test was quantification of C16:0 sulfatides in newborn DBS by ultraperformance liquid chromatography with tandem mass spectrometry (UPLC-MS/MS), with the chosen cut-off (0.17 µM) allowing for 100% sensitivity, which was derived from data from 15 newborns with MLD. The secondary screening test was measurement of ARSA enzymatic activity in DBS from those newborns with abnormal C16:0 sulfatide levels (threshold <20% daily mean activity). Out of 27,335 newborns, 2 newborns screened positive. Confirmatory gene (ARSA) sequencing was performed on the 2 screen-positives, and on 3 further screen-negatives, for variant discovery. The study reported that the assay had almost 100% specificity and an exceptionally low false-positive rate (0.0037%), although the positive and negative predictive values were not reported. Two screen-positive cases were identified using the 2-tier algorithm, which were confirmed as an MLD-affected patient and a heterozygote based on the genetic confirmatory testing.[15]

In summary, only 1 study reported on a 2-tier screening strategy for MLD in newborn DBS samples, followed by genetic ARSA confirmatory testing, which was designed to have 100% sensitivity, and was ultimately found to have almost 100% specificity. A 2-tier screening strategy in DBS samples for MLD is considered the gold standard in minimising false-positives (and avoiding overdiagnosis). However, at present, evidence on the performance of the 2-tier newborn screening strategy in DBS samples for MLD is limited. The completion of 2 ongoing prospective pilot studies in Northern Germany and New York, that were discussed in the annual call submission, should contribute to the availability of evidence on this screening strategy.[21, 22]

By contrast, numerous studies are available that evaluate single screening tests (measurement of sulfatides or enzymatic ARSA activity) followed by genetic confirmatory testing, but did not fulfil the eligibility criteria for this evidence map. Further work on this question to evaluate all available screening strategies would therefore be justified.

## Question 2: What is the volume and type of evidence available on the benefits and/or harms of interventions in presymptomatic/asymptomatic children with MLD through screening?

Of the 1,151 abstracts reviewed, 25 studies were identified for this question. Full-text publications were consulted for 5 of these to determine their relevance. Of these, 19 interventional, cohort and case-control studies were ultimately prioritised for inclusion; the remaining 6 case reports/series (including one case report of treatment with Libmeldy) are not presented or further discussed in this report but are listed for information in Appendix 2. No studies reported on cohorts that were explicitly stated to have been identified through newborn or cascade screening.

Of the 19 included publications for Question 2, there are 14 interventional studies,[11, 19, 23-34] 4 cohort studies[10, 35-37] and 1 case control study.[38] Evaluated interventions included gene therapies (Libmeldy [14 studies],[11, 19, 23-33, 36] and an unnamed vector with intracerebral administration [1 study]),[34] HSCT (3 studies),[10, 37, 38] and umbilical cord blood transplantation (1 study).[35] Where reported, sample size ranged from 2 to 12 presymptomatic patients.[23, 29, 36]

Of the 14 publications reporting on the autologous HSC-GT, Libmeldy, 13 reported on patients with late infantile or early juvenile MLD treated in interventional studies,[11, 19, 23-33] and 1 in a prospective cohort study.[36] Separate findings were reported for those treated while presymptomatic. Reported parameters included ARSA enzymatic levels in blood or cerebrospinal fluid (CSF),[19, 23, 36] MRI,[11, 36] motor skill development and function (including walking ability),[11, 24-33] cognitive development and function,[24, 26, 28, 31-33] disease onset or progression,[19, 23] and survival/mortality.[26, 36]

Three publications specifically reported on the ongoing phase I/II NCT01560182 trial evaluating outcomes in pre-symptomatic children treated with Libmeldy compared with an untreated natural history cohort.[11, 19, 23] Preliminary results of NCT01560182 reported by Biffi 2013 first showed that MLD had not manifested in 3 presymptomatic patients at 7 to 21 months beyond when disease would have been expected to present, based on natural history (follow-up not reported).[23] Sessa 2016, a study included in the annual call submission reporting on NCT01560182, found that ARSA enzymatic activity had been reconstituted in all patients, and that no serious adverse events had occurred (follow-up not reported). Sessa 2016 also reported that MLD onset had been prevented in 7 patients treated pre-symptomatically (although the timepoint was unclear).[19] Fumagalli 2022 reported that among the 5 patients with early juvenile MLD who were treated with Libmeldy while presymptomatic in the NCT01560182 trial, 80% remained event-free in the assessment of severe motor impairment-free survival at 8 years of age, compared with 36% of an untreated natural history cohort.[11] As study identification numbers were not reported in all identified abstracts, it is possible that more of the identified abstracts

reported on the cohort from the NCT01560182 trial (as well as the NCT03392987 trial and 3 EAPs that were used to support the NICE submission for Libmeldy [HST18]).

Across the 11 other publications reporting on studies of Libmeldy (those without clear study identification/trial numbers), 2 publications reported that treatment with Libmeldy restored ARSA enzymatic activity to normal or supranormal levels, at 1 year in 3 evaluable patients being treated under compassionate use,[24] and in a larger prospective cohort of 200 patients being treated under expanded access protocols (unclear follow-up).[36] Development of motor skills and motor function in patients treated with Libmeldy were found to be normal or stable respectively in the majority of treated patients across 10/11 publications, with follow-up ranging from 2 to 11 years post-treatment (where reported).[24-33] In particular, Fumagalli 2022 reported that long-term walking ability was maintained in treated patients (sample size, follow-up or definition of "long-term" was unclear).[33] Normal cognitive development and functioning in patients treated with Libmeldy were also reported by 6 publications,[24, 26, 28, 31-33] with follow-up ranging from 1 to 7.9 years post-treatment. Fumagalli 2017 specifically reported that patients with late-infantile MLD treated with Libmeldy while presymptomatic had better motor and cognitive performance than the untreated natural history cohort, with the 4 early juvenile patients showing normal neurodevelopment, to date (not specified).[31] Two out of the 11 publications reported that there was no observed impact on safety with Libmeldy treatment, with any observed adverse events expected after myeloablative conditioning, supporting that Libmeldy is well tolerated.[24, 26] Specific adverse events were not reported by any of the identified publications. Orchard 2023 reported that all patients had survived,[36] while Fumagalli 2023 reported that 1 presymptomatic patient had died, but that this was not related to Libmeldy treatment (follow-up unclear in both studies).[26]

One interventional study, a clinical phase I/II trial, evaluated intracerebral administration of a gene therapy (different from Libmeldy) with 2 years of follow-up. The study found that while ARSA activity had been restored durably, patients treated before their symptoms manifested still developed MLD, in a way not significantly different than expected considering natural history of the disease.[34]

Three publications reported on HSCT.[10, 37, 38] A case-control study of HSCT in 2 children with late-infantile MLD diagnosed pre-clinically through cascade screening, found that MLD onset was significantly delayed with slower progression (assessment of head-control, and ability to walk aided, crawl and speak) compared with untreated patients.[38] A retrospective cohort study of patients with MLD without cognitive or gross neurological signs found that patients transplanted before symptoms had improved outcomes compared with patients transplanted when symptomatic, including a high intervention-free survival (100% vs 42.9%, p=0.052) and daily living compromise-free survival (although not statistically significant; 66.7% vs 28.6%, p=0.11). It was concluded that HSCT should be given as early as possible before clinical disease onset, with poor results in more advanced or late-infantile patients, highlighting the need for testing of all siblings of index

cases.[10] Yoon 2020, a prospective cohort study, found that HSCT significantly improved the cognitive and language skills in patients treated when asymptomatic, with most of these patients also showing improvement or stabilisation in MRI, nerve conduction velocity, auditory brainstem responses and visual evoked potentials. The results were reported to be long-term based on the title of the publication, but the follow-up period was not reported.[37]

One study evaluated long-term outcomes of umbilical cord blood transplantation in patients with late infantile or early juvenile MLD, including a subgroup of presymptomatic patients.[35] For patients with MLD who received transplant while presymptomatic, some remained normal at follow-up (median 5.1 years) in neurophysiological assessments, gross motor function, and language, although presymptomatic patients were found to have early severe peripheral nerve damage which was either too advanced to be reversed or was not affected by transplantation. The study concluded that children transplanted when asymptomatic benefitted most, but that long-term follow-up of the presymptomatic patients would further clarify whether the neurological disease progression is halted or only delayed by umbilical cord blood transplantation.[35]

In summary, 25 studies reported on the benefit and/or harms of treatments in presymptomatic children with MLD, 6 of which were of lower methodological quality and hence not discussed in this report. None of these studies reported on patient populations identified through newborn screening.

Libmeldy was the most common intervention, and was consistently found to be effective in the majority or all of presymptomatic patients with MLD across the 14 identified publications evaluating this treatment, including for development and stability of motor (11 publications)[11, 24-33] and cognitive function (6 publications)[24, 26, 28, 31-33] at up to 11 years post-treatment. Libmeldy was also found to be safe and well tolerated (3 publications).[19, 24, 26] By contrast, MLD intracerebral gene therapy did not prevent onset of MLD based on 1 identified study.[34] Across the studies assessing HSCT or umbilical cord blood transplant, the interventions were more effective at delaying disease progression compared with symptomatic, treated patients, or untreated patients. However, it is unclear whether these treatments halt progression.

At present, there is sufficient evidence on the effects of treatments for MLD to recommend further work on this question.

## Question 3: What is the volume and type of evidence on the cost-effectiveness of treatment or screening for MLD in asymptomatic or symptomatic patients?

Of the 1,151 abstracts reviewed, 4 studies (reported on by 5 conference abstracts) were included for this question.[13, 39-42]

One study evaluated the cost-effectiveness of newborn screening for MLD compared with no screening.[13] Bean 2022 was a cost-utility analysis, based on a decision-analytic framework using a UK NHS perspective, that was included in the annual call proposal. The modelled population comprised 640,370 live births in England and Wales. At a discount rate of 1.5%, screening for MLD resulted in 790 incremental quality-adjusted life years (QALYs) and an incremental cost-effectiveness ratio (ICER) below £30,000/QALY gained, compared with no screening.[13]

Three studies evaluated the cost-effectiveness of Libmeldy, for the treatment of MLD (including presymptomatic and symptomatic patients) when compared with best supportive care. Of these, 2 studies, conducted from UK and US perspectives, modelled patients with late infantile form (defined as age at symptom onset ≤30 months) or early juvenile (age at symptom onset between 30 months to 6 years) MLD, as well as a combined cohort.[39, 40] In the UK, Libmeldy resulted in 30 incremental QALYs at a discount rate of 1.5% for the combined MLD population, with the resulting ICER below £100,000/QALY gained. From a US perspective, it was concluded that ICERs were substantially lower than the cost-effectiveness thresholds used in multiple jurisdictions, indicating that Libmeldy is a cost-effective use of resources according to US benchmarks.[40] Both studies reported that Libmeldy was most cost-effective for treating presymptomatic patients with MLD. One study, reported on by 2 abstracts,[41, 42] was a cost-effectiveness analysis of Libmeldy compared with best supportive care for the treatment of MLD from a French perspective, concluding that Libmeldy is comparable or better, in terms of cost-effectiveness, than other drugs currently funded for the treatment of rare diseases by the French healthcare system (no willingness-to-pay thresholds are used in France).[41, 42]

In summary, 3 studies evaluated the cost-effectiveness of treatment (all gene therapies) for MLD, and 1 study evaluated the cost-effectiveness of newborn screening for MLD.

Newborn screening for MLD was found to be cost-effective in the UK. Gene therapy with Libmeldy was found to be cost-effective for the treatment of MLD in the UK and US, and was most cost-effective when treating presymptomatic patients. No willingness-to-pay thresholds are used in France, but Libmeldy was also concluded to be comparable or better, in terms of cost-effectiveness, than other drugs funded for treating rare diseases in France.

At present, the volume and type of evidence on the cost-effectiveness of treatment or screening for MLD is currently limited and confined to conference abstracts. However, given the recent reimbursement decision on Libmeldy in the UK by NICE, it is expected that the timeframe for publication of new evidence will be short. As such, further work on the question of cost-effectiveness is also justified.

# Conclusions

On the basis of this evidence map, the volume and type of evidence related specifically to the accuracy of a newborn 2-tier screening strategy for MLD using DBS is limited though promising. Therefore, further work to evaluate all available screening strategies would be justified. The volume and type of evidence related to the benefits and/or harms of treatments in presymptomatic patients with MLD is sufficient to justify a more in-depth review of the evidence. Finally, the volume and type of evidence on the cost-effectiveness of treatment or screening for MLD is currently limited and confined to conference abstracts. However, given the recent reimbursement decision on Libmeldy in the UK by NICE, it is expected that the timeframe for publication of new evidence will be short. As such, further work on the question of cost-effectiveness is also justified.

## Recommendations

On the basis of this evidence map, it is recommended that further work on screening for MLD should be commissioned. Furthermore, given that screening for MLD has not been previously considered by the UK NSC, it is also recommended that MLD should be added to the UK NSC recommendations list.

# Appendix 1 — Search strategy for the evidence map

## Databases and platforms searched

Ovid MEDLINE® In-Process & Other Non-Indexed Citations, Daily and Epub Ahead of Print, Ovid MEDLINE® and Versions 1946 to April 21, 2023, Embase® 1974 to 2022 April 21, the Cochrane Libraries (Cochrane Database of Systematic Reviews, Issue 4 of 12, April 2023; Cochrane Central Register of Controlled Trials, Issue 4 of 12, April 2023), NHD-EED, and the H TA database.

## Search dates

1st January 2012 to 21st April 2023 for MEDLINE and Embase, and to 24th April 2023 for CDSR, CENTRAL, NHD-EED and the HTA Database. All searches were run on 24th April 2023.

## Search strategies

Search terms for MEDLINE and Embase (searched simultaneously via the Ovid SP platform):

1. exp leukodystrophy, metachromatic/ or Exp Metachromatic leukodystrophy/
2. Metachromatic leukodystrophy.ti,ab,kf.
3. (arylsulfatase A deficiency or ARSA deficiency).ti,ab,kf.
4. Or/1-3
5. exp animals/ not exp humans/
6. 4 not 5
7. Limit 6 to yr=2012-current
8. Remove duplicates from 7

Search terms for the Cochrane Libraries (searched via the Wiley Online platform):

1. [mh "leukodystrophy, metachromatic"]
2. (Metachromatic leukodystrophy):ti,ab,kw
3. (arylsulfatase A deficiency or ARSA deficiency):ti,ab,kw
4. {OR #1-#4}
5. #4 in Trials, with publication date from 2012
6. #4 in Reviews, with Cochrane publication date from January 2012

Search terms for NHS-EED (searched via the University of York CRD platform):

1. MeSH DESCRIPTOR leukodystrophic, metachromatic EXPLODE ALL TREES
2. (Metachromatic leukodystrophy)
3. (arylsulfatase A deficiency or ARSA deficiency)

4. #1 or #2 or #3
5. #4 in NHS-EED

Search terms for the HTA database (searched via the INAHTA platform):

1. "Leukodystrophy, Metachromatic"[mhe]
2. "Metachromatic leukodystrophy"
3. (arylsulfatase A deficiency or ARSA deficiency)
4. #1 or #2 or #3
5. #4 with Year from 2012 to 2023

## Numbers of results for each database and question if applicable

MEDLINE and Embase: 1068
Cochrane Libraries: 8
HTA Database: 81
NHS-EED: 0
Total: 1,163
**Total unique results after de-duplication: 1,151**

## Inclusions and exclusions

**Inclusion criteria for Question 1:**

- **Population:** newborns
- **Intervention:** two-tier strategy, using dried blood spots and existing MS/MS technology, to identify individuals with MLD:
  - Abnormal (increased) levels of C16:0-sulfatide
  - ARSA enzymatic activity
  - Newborns with an abnormal increase in C16:0 sulfatide levels and reduced ARSA activity are considered screen positives
- Reference standard: Genetic confirmatory testing or any specific “gold standard”, as determined by the study
- **Comparator:** any or none
- **Outcomes:** sensitivity, specificity, positive and negative predictive values, likelihood ratios, area under the curve, incidental findings e.g., MSD
- **Study design:**
  - Tier 1: SLRs and (N) MAs, interventional studies (e.g., RCTs), observational studies (e.g., cohort studies, case-control studies)
  - Tier 2: Any other primary study design
- **Other considerations:**
  - Abstract or full-text in the English language
  - Published since January 2012

**Inclusion criteria for Question 2:**

- **Population**: presymptomatic/asymptomatic newborns, infants or children with MLD identified through screening, routine clinical diagnosis or other public health interventions
- **Intervention**: atidarsagene autotemcel/ARSA-cel (Libmeldy)
- **Comparator**: no treatment or any other intervention
- **Outcomes**: delay in presentation or reduction in symptoms and mortality associated with MLD, harms of Libmeldy or other interventions, overtreatment, improvement in QoL, any other outcome
- **Study design:**
    - Tier 1: SLRs and (N)MAs, interventional studies (e.g., RCTs), observational studies (e.g., cohort studies, case-control studies)
    - Tier 2: any other primary study design
- **Other considerations:**
    - Abstract or full-text in the English language
    - Published since January 2012

**Inclusion criteria for Question 3:**

- **Population:** newborns, infants or children with MLD
- **Intervention:** atidarsagene autotemcel/ARSA-cel (Libmeldy), any other intervention (e.g., newborn screening, cascade screening)
- **Comparator:**
    - Treatment with atidarsagene autotemcel/ARSA-cel (Libmeldy) or any other intervention following clinical presentation
    - Standard care
    - No treatment or screening/cascade screening
- **Outcomes:** economic evaluations reporting cost-effectiveness outcomes, such as: ICERs, cost per clinical outcome, total QALYs, total disability-adjusted life years (DALYs), total life years gained (LYGs), total costs, incremental costs and QALYs/DALYs
- **Study design:** any of the following study designs:
    - Cost utility, cost-effectiveness, cost-consequence, cost-benefit, cost-minimisation, reviews of economic evaluations (e.g. HTAs), screening models
- **Other considerations:**
    - Abstract or full-text in the English language
    - Published since January 2012

# Appendix 2 – Abstract reporting

## Question 1

### Citation 1

Hong X, Daiker J, Sadilek M, et al. Toward newborn screening of metachromatic leukodystrophy: results from analysis of over 27,000 newborn dried blood spots. Genetics in Medicine 2021;23(3):no pagination[15]

### Study type

Prospective cohort study

### Objectives

To assess the feasibility of screening MLD using DBS from de-identified newborns.

### Components of the study

**Population:** de-identified newborns (screening population) and newborns with MLD (controls)
**Intervention (index test):** quantification of C16:0 sulfatide in DBS by ultraperformance LC-MS/MS (primary test), followed by measurement of ARSA activity in DBS from newborns with abnormal C16:0 sulfatide levels (secondary test) as algorithm A; or ARSA DBS testing followed by C16:0 sulfatide DBS quantification (algorithm B)
**Comparator (reference standard):** ARSA gene sequencing
**Outcomes:** screen positives; screen negatives; incidence of MLD (affected) and heterozygosity, false positive rate, specificity
[full-text consulted]

### Outcomes reported

A total of 27,335 newborns were screened using this two-tier algorithm, and 2 high-risk cases were identified. ARSA gene sequencing identified these two high-risk subjects to be an MLD-affected patient and a heterozygote. The screening cutoff was established based on the results from 15 MLD newborns to achieve 100% sensitivity. Positive predictive value (PPV) and negative predictive value (NPV) were not reported.
[full-text consulted]

### Conclusions

The study demonstrates that newborn screening for MLD is highly feasible in a real-world scenario with near 100% assay specificity [full-text consulted]

# Question 2 – Libmeldy

## Citation 1

Biffi A, Montini E, Lorioli L. Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. Science 2013;341(6148):no pagination[23]

### Study type

Interventional (NCT01560182)

### Objectives

To use and evaluate a lentiviral vector to transfer a functional ARSA gene into HSCs from 3 presymptomatic patients who showed genetic, biochemical, and neurophysiological evidence of late infantile MLD

### Components of the study

**Population:** patients with presymptomatic late infantile MLD
**Intervention:** autologous HSC-GT (Libmeldy)
**Comparator:** No comparator
**Outcomes:** ARSA activity, disease progression

### Outcomes reported

After reinfusion of the gene-corrected HSCs, the patients showed extensive and stable ARSA gene replacement, which led to high enzyme expression throughout hematopoietic lineages and in cerebrospinal fluid. Analyses of vector integrations revealed no evidence of aberrant clonal behaviour. The disease did not manifest or progress in the three patients 7 to 21 months beyond the predicted age of symptom onset

### Conclusions

These findings indicate that extensive genetic engineering of human haematopoiesis can be achieved with lentiviral vectors and that this approach may offer therapeutic benefit for MLD patients.

## Citation 2

Calbi V, Fumagalli F, Sessa M. Lentiviral hematopoietic stem and progenitor cell gene therapy (HSPC-GT) for metachromatic leukodystrophy (MLD): Clinical outcomes from 33 patients. Bone Marrow Transplantation 2020;55:no pagination[25]

### Study type

Interventional

## Objectives

N/A

## Components of the study

**Population:** patients with late infantile or early juvenile MLD, including asymptomatic patients
**Intervention:** autologous HSC-GT (Libmeldy)
**Comparator:** natural history cohort
**Outcomes:** ARSA activity, safety and tolerability, gross motor function, cognitive development

## Outcomes reported

The majority of presymptomatic patients displayed long-term stabilisation of motor function, many within normal range. Other evaluated outcomes were not reported, or not reported separately for presymptomatic patients.

## Conclusions

N/A

# Citation 3

Calbi V, Fumagalli F, Gallo V. Lentiviral haematopoietic stem cell gene therapy for metachromatic leukodystrophy: Results in 5 patients treated under nominal compassionate use. Molecular Genetics and Metabolism 2023;138(2):no pagination (presented at WORLDSymposiumTM 2023)[24]

## Study type

Interventional

## Objectives

N/A

## Components of the study

**Population:** patients with presymptomatic late infantile MLD
**Intervention:** autologous HSC-GT (Libmeldyel)
**Comparator:** no comparator
**Outcomes:** ARSA activity, anti-ARSA antibodies, safety, motor and cognitive function

## Outcomes reported

Three evaluable patients at 1 year post-treatment showed median VCN in peripheral blood mononuclear cells (PBMCs) of 4.18 copies/cell (range 2.01-4.9) and effective transduction of bone marrow progenitors (range 52.92-90.48%). ARSA activity was restored up to supranormal levels in PBMCs starting by day 30 and remained stable in all patients. All patients showed positive anti-ARSA antibodies at low titre early after gene therapy without clinical and safety impact and already spontaneously resolved in 4 patients. Other adverse events reported were expected after myeloablative conditioning. All patients show continuous acquisition of new motor and cognitive skills.

## Conclusions

Data presented in these 5 patients show a safety profile and trend of biological efficacy in line with those of patients treated in the clinical development phase. Additional follow-up is ongoing for clinical efficacy endpoints and long-term safety.

# Citation 4

Essing M, Zambon A, Gallo V. Lentiviral Hematopoietic Stem and Progenitor Cell Gene Therapy for Metachromatic Leukodystrophy (MLD): Clinical Outcomes from 38 Patients. Neuropediatrics 2021;52:SUPPL 1 (presented at the 46th Annual Meeting of the Society for Neuropediatrics)[32]

## Study type

Interventional

## Objectives

N/A

## Components of the study

**Population:** patients with late infantile or early juvenile MLD, including asymptomatic patients
**Intervention:** autologous HSC-GT (Libmeldy)
**Comparator:** no comparator
**Outcomes:** motor and cognitive function, treatment-related mortality, safety, ARSA activity

## Outcomes reported

Most presymptomatic patients displayed long-term stabilisation of motor function, with many maintaining walking capabilities, and normal cognitive development. Other evaluated outcomes were not reported, or not reported separately for presymptomatic patients.

### Conclusions

Data from 38 early-onset MLD patients with up to 7.9 years of follow-up demonstrated that Libmeldy was generally well-tolerated and effective in modifying the disease course of early-onset MLD patients.

## Citation 5

Fumagalli F, Calbi V, De Mattia F, et al. Long-term clinical outcomes of atidarsagene autotemcel (autologous hematopoietic stem cell gene therapy [HSC-GT] for metachromatic leukodystrophy) with up to 11 years follow-up. Molecular Genetics and Metabolism 2023; 138(2):107108[26]

### Study type

Interventional

### Objectives

To compare safety and efficacy outcomes of early-onset MLD patients treated with Libmeldy with an untreated natural history cohort.

### Components of the study

**Population:** patients with early-onset MLD (late infantile or early juvenile), including subgroups of presymptomatic and early-symptomatic patients and untreated control patients with early-onset MLD
**Intervention**: Libmeldy
**Comparator:** no treatment
**Outcomes:** motor and cognitive function; mortality; serious adverse events

### Outcomes reported

The risk of experiencing severe motor impairment or death was significantly reduced in presymptomatic treated patients (late infantile, $p<0.001$; early juvenile, $p=0.049$) compared with untreated controls. Most patients treated presymptomatically displayed normal or stabilised motor function at last follow-up. There were no serious adverse events related to Libmeldy. One presymptomatic patient died; this was considered unrelated to Libmeldy.

### Conclusions

Libmeldy treatment is generally well-tolerated and effective in preserving motor and cognitive function or slowing disease progression in most early-onset MLD. Other evaluated outcomes were not reported, or not reported separately for presymptomatic patients.

## Citation 6

Fumagalli F, Calbi V, Sora MGN, et al. Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access. The Lancet 2022; 399(10322):372-383[11]

### Study type

Interventional (NCT01560182)

### Objectives

To investigate the safety and efficacy of Libmeldy in patients with MLD, compared with an untreated natural history cohort.

### Components of the study

**Population:** 29 paediatric patients with early-onset, including subgroups of presymptomatic and early-symptomatic patients and untreated control patients with early-onset MLD, matched by age and disease subtype
**Intervention**: Libmeldy
**Comparator:** no treatment
**Outcomes:** improvement of more than 10% in total gross motor function measure score at 2 years after treatment in treated patients compared with controls; change from baseline of total PBMC ARSA activity at 2 years after treatment, compared with values before treatment; safety outcomes including adverse events and tolerability of lentiviral transduction

### Outcomes reported

At 8 years of age, an estimated 80% of presymptomatic early juvenile treated patients remained event-free versus 36% for the untreated natural history cohort. MRI total scores for treated patients with presymptomatic early juvenile MLD stabilised at significantly lower levels throughout follow-up than they did for natural history patients (p=0.0001). Other evaluated outcomes were not reported, or not reported separately for presymptomatic patients. [full-text consulted]

### Conclusions

Treatment with Libmeldy resulted in sustained, clinically relevant benefits in children with early-onset MLD by preserving cognitive function and motor development in most patients, and slowing demyelination and brain atrophy

## Citation 7

Fumagalli F, Calbi V, Sessa M, et al. Lentiviral hematopoietic stem cell gene therapy (HSC-GT) for metachromatic leukodystrophy (MLD) provides sustained clinical benefit. Bone Marrow Transplantation 2019;54:76-77[27]

### Study type

Interventional

### Objectives

To assess the safety and efficacy of experimental autologous ex-vivo, lentiviral-mediated HSC-GT treatment of patients with early-onset MLD, followed-up 8-years post treatment.

### Components of the study

**Population:** patients with early-onset MLD, including subgroups of presymptomatic and early-symptomatic patients
**Intervention:** experimental autologous ex-vivo, lentiviral-mediated HSC-GT treatment
**Comparator:** none
**Outcomes:** 10% improvement in GMFM score and increase in ARSA activity in PBMCs evaluated 24 months after treatment; cognitive function; safety endpoints including engraftment failure and long-term safety and tolerability of lentiviral transduction.

### Outcomes reported

The majority of late infantile and early juvenile subjects treated before the onset of overt symptoms showed normal motor development, stabilisation of motor dysfunction or a significant delay in disease progress. Cognitive function was maintained within normal range for most subjects, independent of their symptomatic status at the time of treatment. Other evaluated outcomes were not reported, or not reported separately for presymptomatic patients.

### Conclusions

Presymptomatic treated patients achieved sustained clinical benefit in terms of motor and cognitive function as well as on instrumental biomarkers of PNS and CNS demyelination, suggesting that autologous, ex-vivo HSC-GT is a highly promising therapeutic approach for late infantile and early juvenile MLD presymptomatic subjects.

## Citation 8

Fumagalli F, Calbi V, Sessa M, et al. Lentiviral (LV) Hematopoietic Stem Cell Gene Therapy (HSC-GT) for Metachromatic Leukodystrophy (MLD) Provides Sustained Clinical Benefit. Annals of Neurology 2019;86:S163-S164[28]

### Study type

Interventional (clinical trial and EAP)

### Objectives

To report data of HSC-GT in patients with MLD with 1–8 years follow-up, and a natural history cohort (control).

### Components of the study

**Population**: patients with early-onset MLD, including subgroups of presymptomatic and early-symptomatic patients, and untreated control patients with early-onset MLD
**Intervention**: experimental autologous ex-vivo, lentiviral-mediated HSC-GT treatment
**Comparator**: no treatment
**Outcomes**: pharmacodynamic effects, improvement of motor and cognitive function, and de-myelination process

### Outcomes reported

Presymptomatic treated patients displayed normal motor function or stabilisation/slower progression of motor impairment compared with the natural history cohort. Other evaluated outcomes were not reported, or not reported separately for presymptomatic patients.

### Conclusions

HSC-GT may prevent or stabilise motor and cognitive decline and progressive demyelination and atrophy, particularly when patients are treated before symptom onset.

## Citation 9

Fumagalli F, Calbi V, Sessa M, et al. Lentiviral (LV) Hematopoietic Stem Cell Gene Therapy (HSC-GT) for Metachromatic Leukodystrophy (MLD) Provides Sustained Clinical Benefit. Journal of Inherited Metabolic Disease 2019;42(Supplement 1):7-8[21]

### Study type

Interventional (clinical trial and EAP)

### Objectives

To report data of HSC-GT in patients with MLD with 1–8 years follow-up, compared with an untreated natural history cohort

## Components of the study

**Population:** patients with early-onset MLD, including subgroups of presymptomatic and early-symptomatic patients, and a natural history cohort (control)
**Intervention:** experimental autologous ex-vivo, lentiviral-mediated HSC-GT treatment
**Comparator:** no treatment
**Outcomes:** treatment effects on gross motor function and cognitive development; reconstitution of ARSA activity in haematopoietic system and cerebrospinal fluid; safety endpoints including conditioning-related toxicity and safety and tolerability of gene therapy

## Outcomes reported

Most patients treated before overt symptom onset (eight late infantile and four early juvenile) displayed normal motor function or stabilisation of motor impairment, compared with the natural history cohort, and maintained cognitive performance within normal range. Other evaluated outcomes were not reported, or not reported separately for presymptomatic patients.

## Conclusions

HSC-GT was effective in modifying the disease course of early-onset MLD patients with sustained clinical benefit, particularly in patients treated before onset of overt clinical manifestations.

# Citation 10

Fumagalli F, Calbi V, Sessa M, et al. Lentiviral hematopoietic stem and progenitor cell gene therapy (HSPC-GT) for metachromatic leukodystrophy (MLD): Clinical outcomes from 33 patients. Molecular Genetics and Metabolism 2020;129(2):S59[30]

## Study type

Interventional

## Objectives

To assess safety and efficacy results in patients with early-onset MLD treated with an experimental HSPC-based gene therapy.

## Components of the study

**Population:** patients with early-onset MLD, including subgroups of presymptomatic patients, and a natural history cohort (control)
**Intervention:** experimental HSPC-based gene therapy (Libmeldy) as a fresh or cryopreserved formulation

**Comparator:** no treatment
**Outcomes:** reconstitution of ARSA activity; safety and tolerability of Libmeldy; effects on gross motor function and cognitive development

### Outcomes reported

The majority of presymptomatic patients displayed long-term stabilisation of motor function, many within a normal range. Other evaluated outcomes were not reported, or not reported separately for presymptomatic patients.

### Conclusions

Data from 33 patients with early-onset MLD, with ≤8 years follow-up, show Libmeldy is safe, well tolerated, and effective in modifying the disease course of early-onset MLD patients.

## Citation 11

Fumagalli F, Calbi V, Zambon A, et al. Update on safety and efficacy of lentiviral hematopoietic stem cell gene therapy (HSC-GT) for metachromatic leukodystrophy (MLD). European Journal of Paediatric Neurology 2017;21:e20[31]

### Study type

Interventional

### Objectives

To present an updated ad hoc analysis of patients with early-onset MLD treated with experimental HSC-GT.

### Components of the study

**Population:** patients with early-onset MLD (late infantile or early juvenile), including subgroups of presymptomatic and symptomatic patients and untreated control patients with MLD
**Intervention:** Libmeldy
**Comparator:** no treatment
**Outcomes:** mortality; treatment-related adverse events; abnormal clonal proliferation; ARSA activity in haematopoietic system and cerebrospinal fluid; motor and cognitive performance; neurological pathology

### Outcomes reported

Late-infantile presymptomatic patients showed better motor and cognitive performance compared to the natural history cohort. The four early juvenile, presymptomatic patients

showed normal neurodevelopment, to date. Other evaluated outcomes were not reported, or not reported separately for presymptomatic patients.

### Conclusions

Libmeldy continues to be well-tolerated. Presymptomatic late-infantile patients show a sustained clinical benefit.

## Citation 12

Fumagalli F, Calbi V, Zambon A, et al. Lentiviral haematopoietic stem and progenitor cell gene therapy for metachromatic leukodystrophy (MLD): Clinical outcomes from 38 Patients. Developmental Medicine and Child Neurology 2022; 64 (Supplement 1)[33]

### Study type

Interventional

### Objectives

To compare key endpoints from patients with early-onset MLD treated with HSC-GT treatment (Libmeldy) with an untreated natural history cohort.

### Components of the study

**Population:** patients with early-onset MLD (late-infantile or early juvenile), including subgroups of presymptomatic and symptomatic patients and untreated control patients with MLD
**Intervention:** experimental autologous ex-vivo, lentiviral-mediated HSC-GT treatment
**Comparator:** no treatment
**Outcomes:** mortality; treatment-related serious adverse events; malignancies; abnormal clonal expansion; evidence of replication-competent lentivirus; haematological recovery; stable engraftment and restoration of ARSA activity in haematopoietic system and cerebrospinal fluid; motor and cognitive function

### Outcomes reported

The majority of patients treated presymptomatically maintained long-term walking capability and normal cognitive development. Other evaluated outcomes were not reported, or not reported separately for presymptomatic patients.

### Conclusions

Data from 38 patients with early-onset MLD with up to 7.9 years of follow-up demonstrated that Libmeldy was generally well-tolerated and effective in modifying the disease course of early-onset MLD.

## Citation 13

Orchard PJ, Gupta A, Braun J, et al. Compassionate use of OTL-200 for patients with metachromatic leukodystrophy. Molecular Genetics 2023;138(2):no pagination[35] (presented at WORLDSymposium 2023

### Study type

Prospective cohort

### Objectives

To evaluate Libmeldy on patient expanded access protocols in the USA

### Components of the study

**Population:** patients with MLD, including 2 patients with presymptomatic and 1 with early-symptomatic MLD
**Intervention:** autologous HSC-GT (Libmeldy)
**Comparator:** no comparator
**Outcomes:** motor function (GMFC), neuropsychology outcomes, survival

### Outcomes reported

All patients survive. ARSA levels in peripheral blood cells have been normal to supranormal (range 60.1-400.8; mean 228.7; NL [abbreviation not defined] 21-88 nmol/h/mg). Testing for ARSA antibodies has remained negative. The one-year MRI in the presymptomatic early juvenile patient is stable; others have not reached one year. Protein levels in cerebral spinal fluid were elevated in the symptomatic early juvenile patient (170 mg/dl), but has remained stable at 6 months

### Conclusions

Libmeldy shows promise as a treatment for patients with MLD early in the disease course, with the potential to be safer than HSCT due to minimising allogeneic HSCT related complications and eliminating immune suppression. In addition, levels of ARSA activity may exceed what can be achieved with HSCT

## Citation 14

Sessa M., Lorioli L., Fumagalli F.Lentiviral haemopoietic stem-cell gene therapy in early-onset metachromatic leukodystrophy: an ad-hoc analysis of a non-randomised, open-label, phase 1/2 trial. Lancet 2016;388:10043[19]

### Study type

Interventional (NCT01560182)

## Objectives

To assess the long-term outcomes in a cohort of patients with early-onset metachromatic leukodystrophy who underwent haemopoietic stem cell gene therapy

## Components of the study

**Population:** patients with diagnosed MLD, including subgroups with presymptomatic late infantile, early juvenile, or early-symptomatic juvenile MLD
**Intervention:** Libmeldy
**Comparator:** untreated (in control patients with early-onset disease)
**Outcomes:** safety, motor function, ARSA activity

## Outcomes reported

A progressive reconstitution of ARSA activity in circulating haemopoietic cells and in the cerebrospinal fluid was documented in all patients. 8 patients, 7 of whom received treatment when presymptomatic, had prevention of disease onset or halted disease progression as per clinical and instrumental assessment, compared with historical untreated control patients with early-onset disease. No serious adverse events related to the medicinal product were reported.

## Conclusions

The ad-hoc findings provide preliminary evidence of safety and therapeutic benefit of HSC-GT in patients with early-onset MLD who received treatment in the presymptomatic or very early-symptomatic stage.

# Citation 15

Sevin C, Roujeau T, Cartier N. Intracerebral gene therapy in children with metachromatic leukodystrophy: Results of a phase I/II trial. Molecular Genetics and Metabolism;123(2)[34]

## Study type

Interventional (phase I-II trial)

## Objectives

To describe the results of a phase I-II clinical trial using intracerebral administration of an adeno-associated viral vector serotype rh.10 coding for human ARSA enzyme over a 2-years follow-up

## Components of the study

**Population:** patients with presymptomatic (n=2) or early-symptomatic (n=2) MLD

**Intervention:** intracerebral gene (ARSA) therapy
**Comparator:** no comparator
**Outcomes:** safety (adverse events, serious adverse events), vital parameters, ARSA activity in CSF

### Outcomes reported

Despite long-lasting restauration of ARSA activity, presymptomatic patients developed MLD disease, that was not significantly different from the natural history of the disease. Other evaluated outcomes were not reported, or not reported separately for presymptomatic patients.

### Conclusions

N/A

## Question 2 – HSCT

## Citation 16

Kehrer C, Groeschel S, Doering M. and Krägeloh-Mann I. P286–2065 5-year follow-up in hematopoietic stem cell transplantation in 2 patients with late-infantile metachromatic leukodystrophy in comparison to an untreated cohort. European Journal of Paediatric Neurology 2013; (17), p.S132[38]

### Study type

Case-control

### Objectives

To assess the benefit of infantile HSCT on two girls with late-infantile MLD

### Components of the study

**Population:** two girls with late-infantile MLD who had been diagnosed pre-clinically due to affected siblings, and treated with infantile HSCT, and a natural course cohort of untreated patients
**Intervention:** HSCT
**Comparator:** no treatment
**Outcomes:** motor and cognitive functioning; neurological pathology (MRI-detected)

### Outcomes reported

Aided walking as possible until age 70 months in patient 1 and 48 months in patient 2, whilst untreated patients with late-infantile MLD lost this significantly earlier. Crawling- and head-control was lost at age 72 months in patient 1 and still preserved in patient 2,

which was beyond the untreated group. Patient 1 learned 2-word sentences and can still speak single words, whilst patient 2 speaks in whole sentences. Untreated patients lost complete speech before the age of 4 years old. No MLD-typical lesions were seen in patient 1, but mild de-myelination was observed at 39 months in patient 2, clearly later than the untreated controls.

### Conclusions

HSCT in the presymptomatic stage in late-infantile MLD significantly delays onset and alleviates disease progression compared to untreated patients. However, risk and benefits have to be carefully balanced when considering a severe and invasive therapy.

## Citation 17

Van Rappard DF, Boelens JJ, Van Egmond ME, et al. Efficacy of hematopoietic cell transplantation in metachromatic leukodystrophy: The Dutch experience. Blood 2016;127(24):3098-310110 [full-text was consulted][10]

### Study type

Retrospective cohort

### Objectives

To evaluate effectiveness of H S C T in patients with MLD.

### Components of the study

**Population**: patients with MLD, with an IQ above 70 and without gross neurological signs (i.e., ambulation without support, no dysphagia)
**Intervention**: HSCT
**Comparator**: no HSCT
**Outcomes**: ARSA activity, neurological examination, brain MRI (MLD-Loes score), nerve conduction velocity (NCV), cognitive and motor function, transplantation-related mortality, intervention-free survival (wheelchair dependency, gastrostomy, intrathecal baclogen, or death), daily living-compromise-free survival, overall survival

### Outcomes reported

Symptomatic transplanted patients had lower estimated intervention-free survival (42.9% vs 100%, p=0.052) and lower daily living-compromise-free survival probability (28.6% vs 66.7%, p=0.11) than presymptomatic transplanted patients. Patients (2 with the juvenile form) showed cognitive deterioration, despite presymptomatic HCT, and despite relatively stable white matter changes, suggesting neuronal involvement perhaps less amenable to treatment with HSCT.Other evaluated outcomes were not reported, or not reported separately for presymptomatic patients. [full-text consulted]

## Conclusions

As the best moment for HCT is as early as possible and before clinical disease onset, it is of utmost importance to test all siblings of an index case, including older ones. For more advanced and late-infantile patients, results are discouraging. For the majority of patients evaluated, HCT was no longer an option, nor did they qualify for treatment trials, emphasising the need for earlier diagnosis and better treatment strategies.

# Citation 18

Yoon IC, Bascou NA, Poe MD, and Escolar ML. Long-term neurodevelopmental, neurophysiological, and neuroradiological outcomes of hematopoietic stem cell transplantation for treatment of late-infantile metachromatic leukodystrophy. Molecular Genetics and Metabolism 2020;129(2)[37]

## Study type

Prospective cohort.

## Objectives

Not reported.

## Components of the study

**Population:** patients with MLD, including asymptomatic and symptomatic at the time of treatment
**Intervention:** HSCT
**Comparator:** no comparator
**Outcomes:** neurophysiological and neuroradiological testing (ABR, VEP, NCV, MRI); motor abilities; cognitive and language skills

## Outcomes reported

Asymptomatic patients were significantly improved in cognitive and language skills (compared to symptomatic patients who experienced regression similar to natural history). Most patients' motor abilities did not improve after transplantation with the exception of two asymptomatic patients who continued to gain fine motor skills. Most asymptomatic patients showed improvement or stabilisation in MRI, NCV, ABR, and VEP results.

## Conclusions

HSCT significantly improves the natural progression of MLD in asymptomatic patients. Newborn screening will be needed for early diagnosis and to derive maximal benefit from HSCT.

# Question 2 – Umbilical Cord Transplantation

## Citation 19

Martin HR, Poe MD, Provenzale J. Neurodevelopmental Outcomes of Umbilical Cord Blood Transplantation in Metachromatic Leukodystrophy. Biology of Blood and Marrow Transplantation 2013;19(4):616-62429

### Study type

Retrospective cohort

### Objectives

To evaluate long-term treatment outcomes after unrelated donor umbilical cord blood transplantation in paediatric patients according to disease burden and age at onset (i.e., late-infantile versus juvenile)

### Components of the study

**Population:** patients with late infantile or juvenile MLD, including asymptomatic patients
**Intervention:** umbilical cord blood transplantation
**Comparator:** no comparator
**Outcomes:** motor function (GMFC), neuropsychology outcomes

### Outcomes reported

Neurophysiological studies: 1 asymptomatic patient had normal pretransplant results, which remained normal after transplantation
Gross motor function: In the juvenile-onset group, patients who were asymptomatic at transplantation have borderline motor function
Fine motor function: Of the surviving patients with late-infantile onset who were asymptomatic at baseline, 1 was developing normally, but the other 2 reached a developmental plateau at approximately 2 years of age. Of the 3 asymptomatic juvenile-onset patients, 2 who were assessed post-transplant were developing normally
Cognitive function: In the late-infantile-onset group, the patient treated as an asymptomatic 3-month-old infant continued to gain cognitive skills at a normal rate
Adaptive behaviour: In the late-infantile-onset group, patients who were asymptomatic at the time of transplantation stabilised at the pretransplant level, but the symptomatic patients continued to decline
Language: In the late-infantile-onset group, one patient who was asymptomatic at baseline showed normal language development and the other had skills in the borderline normal range. In the 15 juvenile-onset patients assessed, 3 asymptomatic patients continued to gain skills [full text consulted]

### Conclusions

Children who were asymptomatic at the time of transplantation benefited most from the procedure.

## Question 2 – Deprioritised Studies

### Citation 1

Beschle J, Döring M, Kehrer C, et al. Early clinical course after hematopoietic stem cell transplantation in children with juvenile metachromatic leukodystrophy. Molecular and Cellular Pediatrics 2020;7:1-9.

### Citation 2

Bley A, Müller I, Löbel U, et al. Hematopoietic stem cell transplantation (HSCT) in nine patients with juvenile MLD. Neuropediatrics 2013;44:PS14_1097.

### Citation 3

Chen X, Gill D, Shaw P, et al. Outcome of early juvenile onset metachromatic leukodystrophy after unrelated cord blood transplantation: a case series and review of the literature. Journal of Child Neurology 2016;31:338-344.

### Citation 4

Ding XQ, Bley A, Kohlschütter A, et al. Long-term neuroimaging follow-up on an asymptomatic juvenile metachromatic leukodystrophy patient after hematopoietic stem cell transplantation: Evidence of myelin recovery and ongoing brain maturation. American Journal of Medical Genetics Part A 2012;158:257-260.

### Citation 5

Faqueti L, Iop G, da Silva LAL, et al. A Brazilian patient with late infantile metachromatic leukodystrophy treated with lentiviral hematopoietic stem-cell gene therapy: A report from prenatal diagnosis to early treatment. Molecular Genetics and Metabolism 2023;138:107094.

### Citation 6

Inbar-Feigenberg M, Hewson S, Raiman J. Bone marrow transplantation treatment for a 4year old asymptomatic patient with metachromatic leukodystrophy (MLD). Molecular Genetics and Metabolism 2016;2:S60.

# Question 3

## Citation 1

Bean K, Jones S, Chakrapani A, et al. The Cost-Effectiveness of Newborn Screening for Metachromatic Leukodystrophy (MLD) in the UK. Value in Health 2022;25 (1 Supplement):S79[13]

### Study type

Cost-utility analysis

### Objectives

To determine the cost-effectiveness of newborn screening for MLD vs. no screening from the UK NHS perspective.

### Model type

Decision-analytic framework

### Components of the study

**Population:** live births in England and Wales
**Intervention:** newborn screening screening for MLD
**Comparator:** no screening
**Outcomes:** ICER per QALY

### Model inputs

The epidemiology of MLD and the probabilities used to inform the nodes were derived from clinical experts from the three major MLD referral hospitals in the UK. Model inputs for test characteristics and screening specificity were from published literature. Costs and utilities used to inform long-term outcomes were from several sources including NHS reference costs, Libmeldy clinical trial data, a vignette study based on time trade-off valuations of MLD health state descriptions by members of the UK general public, and the UK EQ-5D-5L value set.

### Outcomes reported

Based on 640,370 live births, screening for MLD resulted in an incremental QALY gain of circa 790 QALYs vs. no screening (at a discount rate of 1.5%). The corresponding ICER was below 30,000/QALY gained.

### Conclusions

Newborn screening for MLD is a cost-effective use of NHS resources, driven by the substantive QALY gain for MLD patients treated presymptomatically.

## Citation 2

Pang F, Dean R, Jensen I, et al. The cost-effectiveness of OTL-200 for the treatment of metachromatic leukodystrophy (MLD) in the US. Molecular Genetics and Metabolism 2023;138(2):no pagination

### Study type

Cost-utility analysis

### Objectives

To demonstrate the framework for determining the long-term cost-effectiveness of an ex vivo gene therapy (Libmeldy) compared to best supportive care for the treatment of MLD in the U S setting.

### Model type

7-state partitioned framework

### Components of the study

**Population:** patients with MLD, including subgroups of patients with late infantile (age at symptom onset <=30 months) and early juvenile (age at symptom onset 30 months to 6 years) variants of MLD
**Intervention:** Libmeldy (ex vivo gene therapy)
**Comparator:** best supportive care
**Outcomes:** ICER per QALY

### Model inputs

Health state transitions were based on patient-level data from Libmeldy clinical trials, and expert opinion. Resource use and clinical assumptions beyond the trial duration were informed by claims database analyses, structured expert elicitation and published literature. Costs included both Commercial and Medicaid estimates. Utilities were from a variety of sources including (i) vignette study based on time trade-off valuations of health state descriptions and (ii) literature searches of analogue disease areas. Caregiver utilities were based on EQ-5D-5L from an international survey.

### Outcomes reported

For the combined MLD population (comprising all variants), base case analysis indicated that Libmeldy is associated with substantial incremental gains in excess of 30 QALYs (at a discount rate of 1.5%). Subgroup analyses indicated Libmeldy was most cost-effective for patients treated presymptomatically.

### Conclusions

This is the first de novo cost-effectiveness study in the US which has considered both the motor and cognitive aspects of MLD and indicates that Libmeldy is a cost-effective use of resources according to US benchmarks.

## Citation 3

Pang F, Dean R, Jensen I, et al. The Cost-Effectiveness of OTL-200 for the Treatment of Metachromatic Leukodystrophy (MLD). Value in Health 2021;24(Supplement 1):S203[40]

### Study type

Cost-utility analysis

### Objectives

To determine the long-term cost-effectiveness of a recently approved ex vivo gene therapy (Libmeldy) compared to best supportive care for the treatment of MLD, using the UK NHS as the base setting.

### Model type

7-state partitioned framework

### Components of the study

**Population:** patients with MLD, including subgroups of patients with late infantile (age at symptom onset <=30 months) and early juvenile (age at symptom onset 30 months to 6 years) variants of MLD
**Intervention:** Libmeldy (ex vivo gene therapy)
**Comparator:** best supportive care
**Outcomes:** ICER per QALY

### Model inputs

Health state transitions were based on patient-level data from Libmeldy clinical trials, and expert opinion. Resource use and clinical assumptions beyond the trial duration were derived through structured expert elicitation. Costs were from a variety of sources

including NHS reference costs. Utilities were from a vignette study based on TTO valuations of health state descriptions by members of the UK general public (n=101). Caregiver utilities were based on EQ-5D-5L from an international survey.

### Outcomes reported

For the combined MLD population (comprising all variants), base case analysis indicated that Libmely is associated with incremental gains in excess of 30 (at a discount rate of 1.5%). The corresponding ICER was below £100,000 per QALY gained. Subgroup analyses indicated Libmeldy was more cost-effective for patients treated presymptomatically.

### Conclusions

This is the first de novo cost-effectiveness study which has considered both the motor and cognitive aspects of MLD and generated ICERs which are substantially lower than the cost-effectiveness thresholds used in a number of jurisdictions, indicating that Libmeldy is a cost-effective use of resources.

## Citation 4 and 5

Pang F, Dean R, Jensen I, et al. The Cost-Effectiveness of Atidarsagene Autotemcel for the Treatment of Metachromatic Leukodystrophy (MLD) in France. Value in Health 2022;25(7 Supplement):S339[41]

Pang F, Dean R, Jensen I, et al. The cost-effectiveness of atidarsagene autotemcel for the treatment of metachromatic leukodystrophy in France. Molecular Genetics and Metabolism 2022;135(2):S93[42]

### Study type

Cost-utility analysis

### Objectives

To determine the cost-effectiveness of a definitive ex vivo gene therapy, Libmeldy, compared to best supportive care for the treatment of MLD from the French perspective.

### Model type

7-state partitioned framework

### Components of the study

**Population:** patients with MLD, including subgroups of patients with late infantile (age at symptom onset <=30 months) and early juvenile (age at symptom onset 30 months to 6 years) variants of MLD
**Intervention:** Libmeldy

**Comparator:** best supportive care
**Outcomes:** ICER per QALY

## Model inputs

Resource use and clinical assumptions beyond the trial duration were derived through structured expert elicitation. Costs were from a variety of sources including the French national databases on Hospital costs (PMSI), Biological Procedures (NABM) and official tariffs for medical visits (AMELI). Utilities to derive quality of life of the health states were from a vignette study based on time trade-off valuations of health state descriptions. Caregiver utilities were based on EQ-5D-5L from an international caregiver survey including French respondents.

## Outcomes reported

For the combined MLD population (comprising late infantile and early juvenile), base case analysis indicated that Libmeldy is associated with incremental gains in excess of 28 QALYs (discount rate of 2.5% for first 30 years then 1.5%).

## Conclusions

There are no official cost-effectiveness thresholds in France. However, the study shows that Libmeldy has comparable or better cost-effectiveness estimates than other drugs for rare diseases that are currently funded by the French health system.

# References


1. Gomez-Ospina N. Arylsulfatase A Deficiency. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, eds. GeneReviews(®). Seattle (WA): University of Washington, Seattle
Copyright © 1993-2023, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved., 2020.
2. Shaimardanova AA, Chulpanova DS, Solovyeva VV, et al. Metachromatic Leukodystrophy: Diagnosis, Modeling, and Treatment Approaches. Front Med (Lausanne) 2020;7:576221.
3. Great Ormond Street Hospital for Children NHS Foundation Trust. Metachromatic Leukodystrophy (Late Infantile Form). In: Trust GNF, ed, 2016.
4. National Institute of Neurological Disorders and Stroke. Metachromatic Leukodystrophy. Available at: https://www.ninds.nih.gov/health-information/disorders/metachromatic-leukodystrophy#:~:text=The%20prognosis%20for%20MLD%20is,years%20following%20onset%20of%20symptoms. Last accessed: 07/06/2023.
5. Excellence NIfHaC. Atidarsagene autotemcel for treating metachromatic leukodystrophy (HST18) [Available at: https://www.nice.org.uk/guidance/hst18/chapter/1-Recommendations]. Highly specialised technologies guidance, 2022.
6. Mayo Clinic. Metachromatic leukodystrophy [Available at: https://www.mayoclinic.org/diseases-conditions/metachromatic-leukodystrophy/symptoms-causes/syc-203547330 Last Accessed: 30.05.23], 2020.
7. Laugwitz L, Santhanakumaran V, Spieker M, et al. Extremely low arylsulfatase A enzyme activity does not necessarily cause symptoms: A long-term follow-up and review of the literature. JIMD Rep 2022;63:292-302.
8. Boucher AA, Miller W, Shanley R, et al. Long-term outcomes after allogeneic hematopoietic stem cell transplantation for metachromatic leukodystrophy: the largest single-institution cohort report. Orphanet J Rare Dis 2015;10:94.
9. Blenda AV. Metachromatic Leukodystrophy Treatment & Management. Available at: https://emedicine.medscape.com/article/951840-treatment [Last accessed 30/05/23/]. In: Medscape, ed, 2021.
10. Van Rappard DF, Boelens JJ, Van Egmond ME, et al. Efficacy of hematopoietic cell transplantation in metachromatic leukodystrophy: The Dutch experience. Blood 2016;127(24):3098-3101.
11. Fumagalli F, Calbi V, Natali Sora MG, et al. Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access. Lancet 2022;399:372-383.
12. Genomics Education Programme. A ground-breaking new gene therapy has saved the life of its very first NHS patient. Available at: https://www.genomicseducation.hee.nhs.uk/blog/a-ground-breaking-new-gene-therapy-

has-saved-the-life-of-its-very-first-nhs-patient/#:~:text=Teddi%20and%20Nala,be%20eligible%20for%20the%20treatment. Accessed 12/06/2023., 2023.
13. Bean K, Jones S, Chakrapani A, et al. POSB95 The Cost-Effectiveness of Newborn Screening for Metachromatic Leukodystrophy (MLD) in the UK. Value in Health 2022;25(1 Supplement):S79.
14. Harrington M, Whalley D, Twiss J, et al. Insights into the natural history of metachromatic leukodystrophy from interviews with caregivers. Orphanet Journal of Rare Diseases 2019;14:1-10.
15. Hong X, Daiker J, Sadilek M, et al. Toward newborn screening of metachromatic leukodystrophy: results from analysis of over 27,000 newborn dried blood spots. Genetics in Medicine 2021;23(3):555-561.
16. Hong X, Kumar AB, Daiker J, et al. Leukocyte and dried blood spot arylsulfatase A assay by tandem mass spectrometry. Analytical chemistry 2020;92:6341-6348.
17. Kehrer C, Blumenstock G, Gieselmann V, et al. The natural course of gross motor deterioration in metachromatic leukodystrophy. Developmental Medicine & Child Neurology 2011;53:850-855.
18. Kehrer C, Elgün S, Raabe C, et al. Association of age at onset and first symptoms with disease progression in patients with metachromatic leukodystrophy. Neurology 2021;96:e255-e266.
19. Sessa M, Lorioli L, Fumagalli F, et al. Lentiviral haemopoietic stem-cell gene therapy in early-onset metachromatic leukodystrophy: an ad-hoc analysis of a non-randomised, open-label, phase 1/2 trial. The Lancet 2016;388(10043):476-487.
20. Spacil Z, Kumar AB, Liao HC, et al. Sulfatide analysis by mass spectrometry for screening of metachromatic leukodystrophy in dried blood and urine samples. Clinical Chemistry 2016;62(1):279-286.
21. Schwarz M, Oliva, P, Mechtler, T, Streubel, B, Chanson, C, Essing, MM, Santer, R, Kasper, D. Newborn Screening for Metachromatic Leukodystrophy in Northern Germany – A prospective study. Presented at WORLD symposium 2021 2021.
22. Wasserstein M, Caggana M, Gelb MH, et al. ScreenPlus: a comprehensive, dynamic, multi-disorder newborn screening pilot program. Molecular Genetics and Metabolism 2020;129:S160.
23. Biffi A, Montini E, Lorioli L, et al. Lentiviral hematopoietic stem cell gene therapy benefits metachromatic leukodystrophy. Science 2013;341(6148) (no pagination).
24. Calbi V, Fumagalli F, Gallo V, et al. Lentiviral haematopoietic stem cell gene therapy for metachromatic leukodystrophy: Results in 5 patients treated under nominal compassionate use. Molecular Genetics and Metabolism 2023;Conference: WORLDSymposiumTM 2023. Orlando United States. 138(2) (no pagination).
25. Calbi V, Fumagalli F, Sessa M, et al. Lentiviral hematopoietic stem and progenitor cell gene therapy (HSPC-GT) for metachromatic leukodystrophy (MLD): Clinical outcomes from 33 patients. Bone Marrow Transplantation 2020;55:72-73.
26. Fumagalli F, Calbi V, De Mattia F, et al. Long-term clinical outcomes of atidarsagene autotemcel (autologous hematopoietic stem cell gene therapy [HSC-GT]

for metachromatic leukodystrophy) with up to 11 years follow-up. Molecular Genetics and Metabolism 2023;Conference: WORLDSymposiumTM 2023. Orlando United States. 138(2) (no pagination).
27. Fumagalli F, Calbi V, Sessa M, et al. Lentiviral hematopoietic stem cell gene therapy (HSCGT) for metachromatic leukodystrophy (MLD) provides sustained clinical benefit. Bone Marrow Transplantation 2019;54:76-77.
28. Fumagalli F, Calbi V, Sessa M, et al. Lentiviral (LV) hematopoietic stem cell gene therapy (HSC-GT) for metachromatic leukodystrophy (MLD) provides sustained clinical benefit. Annals of Neurology 2019;86(Supplement 23):S163-S164.
29. Fumagalli F, Calbi V, Sessa M, et al. Lentiviral (LV) hematopoietic stem cell gene therapy (HSC-GT) for metachromatic leukodystrophy (MLD) provides sustained clinical benefit. Journal of Inherited Metabolic Disease 2019;42(Supplement 1):7-8.
30. Fumagalli F, Calbi V, Sessa M, et al. Lentiviral hematopoietic stem and progenitor cell gene therapy (HSPC-GT) for metachromatic leukodystrophy (MLD): Clinical outcomes from 33 patients. Molecular Genetics and Metabolism 2020;129(2):S59.
31. Fumagalli F, Calbi V, Zambon A, et al. Update on safety and efficacy of lentiviral hematopoietic stem cell gene therapy (HSC-GT) for metachromatic leukodystrophy (MLD). European Journal of Paediatric Neurology 2017;21(Supplement 1):e20.
32. Essing M, Zambon A, Gallo V, et al. Lentiviral Hematopoietic Stem and Progenitor Cell Gene Therapy for Metachromatic Leukodystrophy (MLD): Clinical Outcomes from 38 Patients. Neuropediatrics. Conference: 46th Annual Meeting of the Society for Neuropediatrics. Salzburg Austria 2021;52.
33. Fumagalli F, Calbi V, Zambon A, et al. Lentiviral haematopoietic stem and progenitor cell gene therapy for metachromatic leukodystrophy (MLD): Clinical outcomes from 38 Patients. Developmental Medicine and Child Neurology 2022;64(SUPPL 1):55-56.
34. Sevin C, Roujeau T, Cartier N, et al. Intracerebral gene therapy in children with metachromatic leukodystrophy: Results of a phase I/II trial. Molecular Genetics and Metabolism 2018;123(2):S129.
35. Martin HR, Poe MD, Provenzale JM, et al. Neurodevelopmental Outcomes of Umbilical Cord Blood Transplantation in Metachromatic Leukodystrophy. Biology of Blood and Marrow Transplantation 2013;19(4):616-624.
36. Orchard PJ, Gupta A, Braun J, et al. Compassionate use of OTL-200 for patients with metachromatic leukodystrophy. Molecular Genetics and Metabolism 2023;Conference: WORLDSymposiumTM 2023. Orlando United States. 138(2) (no pagination).
37. Yoon IC, Bascou NA, Poe MD, et al. Long-term neurodevelopmental, neurophysiological, and neuroradiological outcomes of hematopoietic stem cell transplantation for treatment of late-infantile metachromatic leukodystrophy. Molecular Genetics and Metabolism 2020;129(2):S164-S165.
38. Kehrer C, Groeschel S, Doering M, et al. 5-year follow-up in hematopoietic stem cell transplantation in 2 patients with late-infantile metachromatic leukodystrophy in

comparison to an untreated cohort. European Journal of Paediatric Neurology 2013;1):S132.
39. Pang F, Dean R, Jensen I, et al. The cost-effectiveness of OTL-200 for the treatment of metachromatic leukodystrophy (MLD) in the US. Molecular Genetics and Metabolism 2023;Conference: WORLDSymposiumTM 2023. Orlando United States. 138(2) (no pagination).
40. Pang F, Dean R, Jensen I, et al. PRO30 The Cost-Effectiveness of OTL-200 for the Treatment of Metachromatic Leukodystrophy (MLD). Value in Health 2021;24(Supplement 1):S203.
41. Pang F, Dean R, Jensen I, et al. The Cost-Effectiveness of Atidarsagene Autotemcel for the Treatment of Metachromatic Leukodystrophy (MLD) in France. Value in Health 2022;25(7 Supplement):S339.
42. Pang F, Dean R, Jensen I, et al. The cost-effectiveness of atidarsagene autotemcel for the treatment of metachromatic leukodystrophy in France. Molecular Genetics and Metabolism 2022;135(2):S93.