Newborn screening for metachromatic leukodystrophy (MLD) in the NHS Newborn Blood Spot (NBS) screening programme: An evidence summary

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PLAIN ENGLISH SUMMARY

When a new population screening programme is proposed, in the UK, it is assessed using the UK National Screening Committee (UK NSC) criteria for appraising its viability, effectiveness and appropriateness. The overall goal of population screening programmes is to provide early treatment or intervention to someone identified as having a condition or risk factor before they have symptoms. Ideally this should lead to better outcomes than if the person were to present later with symptoms. In the UK, the current newborn blood spot screening (NBS) programme looks for nine rare, but serious conditions. Screening uses drops of blood, collected from an infant's heel onto a special card (also known as the 'heel prick test'). In the rare event that laboratory tests on this blood find an abnormal result, the child undergoes further testing to confirm whether they definitely do have one of the conditions screened for. If a child is then diagnosed with one of the conditions, they are referred for treatment.

Metachromatic leukodystrophy (MLD) is a rare inherited condition, which results in nerve damage and progressive symptoms, including muscle weakness, clumsiness, cognitive decline, leading to early death. MLD has three forms which are classified according to age at symptom onset: late infantile (typically presenting before 30 months of age), juvenile (typically presenting between 3 and 16 years of age), and adult (typically presenting after 16 years of age). The late infantile form is the most severe and most common form of MLD and represents 50-60% of cases. Historically, treatments for MLD have been limited to management of symptoms and, for the late infantile form, focussed on palliative care.

In 2022, the National Institute for Health and Care Excellence (NICE) in England approved a new treatment for MLD (Libmeldy®). This treatment is a type of gene therapy and it involves removing and correcting a patient's stem cells by inserting a functional copy of the faulty gene, before returning the cells to the patient.

Libmeldy® is only recommended for the treatments of children with MLD who have not yet developed symptoms or whose symptoms are still at an early stage. However, currently, MLD is not usually detected until symptoms have developed, unless there is an older sibling with the disease or a known family history. This difficulty in establishing an early diagnosis may limit the opportunity for treating children who have no known family members with MLD.

Routine NBS screening for MLD is not currently recommended by the UK NSC in the UK. The addition of screening for MLD to the UK NBS screening programme was proposed in 2021. This review will summarise the evidence, for consideration by the UK NSC, about:

- How many babies with MLD may be missed by screening tests and how many well babies may be wrongly identified as possibly having MLD
- Whether treatment works better when babies are identified (through screening) and treated early
- Whether NBS screening for MLD is value for money

BACKGROUND

THE CONDITION

Metachromatic leukodystrophy (MLD), also known as Arylsulfatase A deficiency (ARSA), is a rare neurodegenerative disease, in which deficiency in the ARSA enzyme leads to accumulation of sulfatides and consequent damage to the myelin sheath of neurons.[1, 2] MLD is a lysosomal storage disorder with autosomal recessive inheritance.[1, 2] The incidence of MLD in the UK has been estimated at approximately 1:40,000 live births.[3] MLD has three forms which are classified according to age at symptom onset: late infantile (typically presenting before 30 months of age), juvenile (typically presenting between 3 and 16 years of age), and adult (typically presenting after 16 years of age).[1] The late infantile form is the most severe and most common form of MLD, comprising 50-60% of cases. Rapid progression of the late infantile form of MLD usually results in death before the age of five years.[2, 4] Approximately 20-25% of children with MLD are affected by the juvenile form, which is typically fatal before the age of 20 years.[5, 6] The adult form of MLD is the least common, with slower progression, characterised by periods of stability and progression continuing until death (typically occurring between 6 and 14 years after diagnosis).[1, 4] The presenting symptoms of MLD vary by form and include muscle weakness, hypotonia, clumsiness, dysarthia, cognitive regression and neurological issues (weakness and loss of coordination progressing to spasticity and incontinence).[1] Individuals with juvenile or adult forms may present with a decline in school or job performance, behavioural or emotional problems, or psychosis.[1]

SCREENING AND DIAGNOSIS

Screening for MLD utilises the measurement of sulfatide levels in urine or dried blood spot (DBS) samples and can also include the measurement of ARSA enzymatic activity in DBS samples. Studies have assessed sulfatide analysis and ARSA enzymatic activity individually (single tier screening),[7, 8] or in combination as a 2-tier screening strategy.[9-11] The 2-tier screening strategy can also identify individuals with multiple sulfatase deficiency (MSD), another ultra-rare lysosomal storage disorder.[9, 12] The treatment options for individuals with MSD are limited to management of symptoms and supportive care.[13] Early identification may be useful for reproductive planning, as carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible using molecular genetic techniques if the pathogenic variants in the family are known.[13] Low ARSA enzymatic activity alone is not considered sufficient for the diagnosis of MLD. This is due to the relatively high prevalence of the ARSA pseudodeficiency allele, which leads to reduced enzyme activity (5 to 20% of that of normal controls),[1] but which is not known to manifest as disease or neurological symptoms.[14] Genetic testing is generally recommended to confirm a diagnosis of MLD and genetic confirmatory testing is considered the reference standard for screening. [2] Magnetic resonance imaging (MRI) brain scans can also be used to inform a diagnosis of MLD.[2]

MLD is usually detected after birth and once symptoms have manifested, unless there is an awareness of family history/mutation status or previous development of MLD in a sibling.[5, 15]

CURRENT TREATMENTS

Interventions evaluated for the treatment of MLD have included bone marrow or haematopoietic stem cell transplantation (HSCT), enzyme replacement therapy, cell therapies and gene therapies.[16] However, HSCT has been shown to have limited efficacy and is associated with a significant risk of complications.[17] Historically, best supportive care and the management of symptoms have been the main focus of treatment, particularly for individuals with late infantile MLD in whom disease management has focussed on palliative care.[5, 15]

Atidarsagene autotemcel (ARSA-cel/OTL-200, developed by Orchard Therapeutics and branded as Libmeldy®) is recommended by the National Institute for Health and Care Excellence (NICE), Highly Specialised Technology guidance (HST18), as an option for treating MLD in presymptomatic children with late infantile or early juvenile MLD, and in children with early juvenile MLD who have early clinical signs or symptoms (who can still walk independently and who have no cognitive decline).[5] Libmeldy® is an autologous haematopoietic stem cell gene therapy (HSC-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.[5] Libmeldy® should be delivered in a highly specialised service by a specialist multidisciplinary team.[5]

The first baby to be treated with Libmeldy® in the UK NHS was treated at the Royal Manchester Children's Hospital in 2022.[18] Treatment began with stem cell harvest at 12 months of age and transplant of the treated stem cells took place in August 2022. The patient was discharged home in October 2022 and, several months later (February 2023), "has fully recovered from the transplant and is showing no signs of the devastating disease she was born with."[19]

Libmeldy® was approved by the U.S. Food and Drug Administration (FDA) for the treatment of presymptomatic late infantile, presymptomatic early juvenile or early symptomatic early juvenile MLD in March 2024.[20]

Current guidance

Routine newborn screening for MLD is not currently recommended by the UK NSC in the UK. Screening was discussed during the appraisal process which informed NICE guidance HST18[5] where clinical and patient experts highlighted the importance of early diagnosis and NBS screening for inherited disorders such as MLD, and NICE appraisal committee's members acknowledged the difficulties of diagnosis without knowledge of an affected sibling.[5, 15]

There is a simple discount patient access scheme for Libmeldy® in place in the national health service (NHS) in England, which is scheduled for review in 2025.[5]

MLD is not included in the Recommended Uniform Screening Panel (RUSP) in the US,[21] and is not included in the list of conditions nominated to the RUSP.[22]

Rationale for this evidence summary

Screening for MLD has not previously been considered by the UK NSC. It was proposed as a potential NBS screening programme in the 2021 annual call for topics. The submission reasoned that, without screening, affected individuals are only identified before symptom

onset when an older sibling is affected and that this limits the opportunity for treatment in individuals without affected siblings. In 2023, a preliminary evidence map was commissioned by the UK NSC to evaluate the volume and type of evidence related to newborn screening for MLD. The evidence map[15] considered the following questions:

- What is the volume and type of evidence on the accuracy of newborn screening strategies for MLD using dried blood spots?
- 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?
- What is the volume and type of evidence on the cost-effectiveness of treatment or screening for MLD in asymptomatic or symptomatic patients?

The 2023 UK NSC evidence map included 25 references, the majority of which (19 references) related to the treatment question.[15] The evidence map included one US study which evaluated a 2-tier screening algorithm (combining quantification of C16:0 sulfatides with measurement of ARSA enzymatic activity) for MLD screening using dried blood spots from 27,000 newborns. The evidence map also noted that two prospective pilot studies were ongoing in Northern Germany and in New York State, US. For the treatment question, publications relating to 19 cohort and case-control studies were included. The interventions evaluated in these studies included gene therapy (most commonly Libmeldy®, 14 publications), HSCT and umbilical cord blood transplantation. These publications evaluated the efficacy and safety of treatments in presymptomatic patients with MLD and included some comparisons of outcomes with untreated or symptomatic treated patients. However, none of the studies included in the evidence map reported cohorts that were explicitly stated to have been identified through NBS screening or cascade testing, i.e. no studies were identified which could provide information on the relative efficacy of a given treatment in early (screening or cascade testing) vs. late (symptomatic clinical detection) diagnosed patients with MLD. Four studies, reported in five conference abstracts, were included for the cost-effectiveness question; three studies evaluated the cost-effectiveness of treatment with Libmeldy® and one study evaluated the cost-effectiveness of NBS for MLD.

The evidence map concluded that there was sufficient evidence to justify commissioning an evidence summary and that MLD should be added to the UK NSC's recommendation list, to be kept under regular review. The evidence provided by the evidence map was presented and discussed by the UK NSC in June 2023. The committee agreed with the conclusions of the evidence map and recommended that further work on screening for MLD should be commissioned in the form of a full evidence summary including all the questions examined by the evidence map.[15]

This evidence summary will inform the further consideration of NBS screening for MLD by the UK NSC and will focus on the evidence available to assess four key UK NSC criteria:[23]

Criterion 4 - There should be a simple, safe, precise and validated screening test.

Criterion 5 - The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

Criterion 9 - There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered.

Criterion 14 - The opportunity cost of the screening programme (including, testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource.

In order to maintain relevance to current practice, and for consistency with the 2023 UK NSC evidence map,[15] this evidence summary will include relevant literature since January 2012. It should also be noted, when considering the references included in the evidence map, that all five references included for the cost-effectiveness question and over half of the references included for the treatment question were conference abstracts and, therefore, do not meet the inclusion criteria specified for the evidence summary.

OBJECTIVES

The overall aim of this review is to assess the volume, type and direction of evidence relevant to newborn screening for MLD. The following key questions have been defined to address this aim:

1. What is the accuracy of single test and 2-tier NBS screening strategies for MLD, using DBS samples?
2. Does early initiation of treatment following screening lead to improved outcomes for MLD compared to initiation of treatment following clinical presentation?
3. How have modelling studies and cost-effectiveness analyses addressed NBS screening for MLD in the era of novel treatments?

In addition to summarising the available evidence to inform the above questions, our report will include:

- An evidence map/horizon scanning section describing ongoing studies and developments in novel therapies for MLD
- A summary of any existing NBS screening programmes for MLD that are relevant to the UK context
- A summary of any published clinical guidelines on the management of MLD that are relevant to the UK context

METHODS

The systematic review will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care, [24] and the Cochrane Handbook[25] and Cochrane Handbook for Diagnostic Test Accuracy Reviews. [26]

INCLUSION CRITERIA

Separate inclusion criteria have been developed for each of the three key questions and these are summarised in Table 1.

Studies published in languages other than English will be excluded. Only studies reported in peer reviewed publications will be included; conference abstracts will be excluded. Where studies reported in conference abstracts and identified by the evidence map meet the inclusion criteria specified for this evidence summary, but have not subsequently been published in full, this will be noted in the report.

Table 1: Inclusion criteria

Key question	**1. What is the accuracy of single test and 2-tier NBS screening strategies for MLD, using DBS samples?**	**2. Does early treatment of MLD, following screening, lead to improved outcomes compared to initiation of treatment following clinical presentation?***	**3. How have modelling studies and cost-effectiveness analyses assessed addressed NBS screening for MLD in the era of novel treatments?**
Population	Newborns	Newborns, infants or children with MLD	Newborns
Intervention	Any screening strategy using DBS samples and single or 2-tier testing to detect MLD	Treatment with Atidarsagene (also called Libmeldy®) or any other intervention, where: 1. MLD has been detected through population screening 2. MLD has been detected in the presymptomatic period (e.g. incidentally or through cascade testing)	Newborn population screening for MLD
Comparator	None or other screening strategy using DBS samples to detect MLD	Treatment with Atidarsagene (also called Libmeldy®) or any other intervention, where: 1. MLD has been detected without population screening 2. MLD has been detected following symptomatic presentation	No newborn screening for MLD or cascade screening

Reference standard	Confirmatory genetic testing or any specified reference standard	NA	NA
Outcomes	Sensitivity, specificity, PPV, NPV, of the screening strategy (e.g. by screening test, method of analysis, single or 2-tier testing and threshold) for the target condition MLD Incidental findings (e.g. MSD)	Survival, symptoms associated with MLD, safety (e.g. incidence of AE associated with treatment), overtreatment, HRQoL, any other reported outcome	Total cost of screening for MLD, incremental cost, incremental life-years gained, gain in any other reported clinical outcome, ICER, number of lives saved, cost per life saved, any other reported outcome
Study design**	Studies in randomly assigned or consecutively enrolled populations (diagnostic cohort studies) and diagnostic case-control studies.	Any comparative study design, in humans, regression analyses where treatment outcome is the dependent variable and diagnostic route (e.g. screening/pre-symptomatic detection/symptomatic detection) or time to treatment is an independent variable.	Decision analytic models and economic evaluations. Cost-minimisation, cost-effectiveness, cost-utility, cost-benefit and cost-consequence analyses. Reviews of economic evaluations.

*If no studies are identified which explicitly compare the efficacy of treatments for MLD in early (screening or cascade testing) vs. late (symptomatic presentation) detection, studies comparing the treatment of presymptomatic people with MLD to no treatment (natural history) or treatment of symptomatic MLD, and studies assessing correlation between time to treatment and outcome will be included.

**Inclusion will not be limited by study setting, however the synthesis will give precedence to studies conducted in the U.K. or locations considered most likely to be applicable to the UK setting (e.g. European Economic Area, the U.S. Canada, Australia and New Zealand)

AE: adverse events; DBS: dried blood spot; HRQoL: Health-Related Quality of Life; ICER: incremental cost-effectiveness ratio; MLD: metachromatic leukodystrophy; MSD: multiple sulfatase deficiency; NA: not applicable; NBS: newborn screening; NPV: negative predictive value; PPV: positive predictive value

LITERATURE SEARCHES

Search strategies will be developed to identify studies on MLD, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[24] and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.[26]

Candidate search terms will be identified from target references, browsing database thesauri (e.g. MEDLINE MeSH and Embase EMTREE), existing reviews and initial scoping searches. Strategy development will involve an iterative approach testing candidate text and indexing terms across a sample of bibliographic databases, aiming to reach a satisfactory balance of sensitivity and specificity. Search strategies will be developed specifically for each database and the keywords and thesaurus terms will be adapted according to the configuration of each database.

In order to maintain relevance to current clinical practice and consistency with the UK NSC 2023 evidence map,[15] searches will be date limited to January 2012 - present. An example search strategy is presented in Appendix 1. This may be adapted following consultation with clinical experts.

Searches will be conducted on the following resources:

- MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily (Ovid)
- EMBASE (Ovid)
- CINAHL (EBSCO)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- International HTA Database (Internet) (https://database.inahta.org/)
- KSR Evidence (KSR Ltd) (Internet) (https://ksrevidence.com/)
- Orphanet (Internet) (https://www.orpha.net/en/disease)
- Orphanet Newborn Screening Bibliographical Knowledgebase (Internet) (https://nbs.orphanet.app/)

Completed and ongoing trials will be identified by searches of the following resources:

- NIH ClinicalTrials.gov (Internet) (http://www.clinicaltrials.gov/)
- EU Clinical Trials Register (Internet) (https://www.clinicaltrialsregister.eu/ctr-search/search)
- WHO International Clinical Trials Registry Platform (ICTRP) (Internet) (http://www.who.int/ictrp/en/
- ScanMedicine (Internet) (https://scanmedicine.com/)

Additional searches

A search of the following resources will be conducted to identify background, guideline and policy documents on MSD:

- Trip Database (Internet) (https://www.tripdatabase.com/)
- Guidelines International Network (GIN) (Internet) (https://g-i-n.net/international-guidelines-library/)
- National Institute for Health and Care Excellence (NICE) (Internet) (https://www.nice.org.uk/)
- NIHR Health Technology Assessment (HTA) (Internet) (https://www.nihr.ac.uk/)
- ECRI Guidelines Trust (Internet) (https://home.ecri.org/)

The main Embase strategy for each search will be independently peer reviewed by a second information specialist based on the CADTH Peer Review checklist.[27]

Reference checking

The bibliographies of included primary studies and systematic reviews will be checked for relevant studies.

Handling of citations

Identified references from the bibliographic database searches will be downloaded into Endnote bibliographic management software for further assessment and handling. Individual records within the Endnote libraries will be tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enables the information specialist to track the origin of each individual database record, and its progress through the screening and review process.

STUDY SELECTION AND DATA EXTRACTION

Two reviewers will independently screen titles and abstracts of all reports identified by the searches and any discrepancies will be resolved by discussion or consultation with a third reviewer. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available, data will be extracted on the following: study design/details; study setting (country); population (e.g. details of screening program/numbers screened, any subgroups reported); details of MLD screening strategy (e.g. including details of sample collection/timing, threshold, manufactures of any commercial kits used, analysis methods, single or 2-tier testing); screening test performance outcome measures (sensitivity and specificity, positive and negative predictive values, details of MLD findings and any incidental findings); details (including timing) of treatment (e.g. Libmeldy®) in intervention and comparator groups; follow-up duration (treatment studies only); treatment outcomes; cost-effectiveness-related outcomes (e.g. ICER, cost per life saved). Data will be extracted by one

reviewer, using piloted data extraction forms. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

Assessment of methodological quality

The methodological quality of any included RCTs of treatment will be assessed using the revised Cochrane Risk of Bias Tool for Randomised Trials (RoB 2)[28] and cohort studies of treatment will be assessed using the ROBINS-I tool.[29] Diagnostic accuracy studies and studies from which accuracy outcomes have been extracted will be assessed using QUADAS-2.[30] Cost-effectiveness studies, will be assessed using the Drummond checklist.[31] Other study designs will be assessed using appropriate tools, as appropriate. Assessment of methodological quality will include consideration of the applicability of studies to the UK setting.

Data synthesis

Based on the reported findings of the 2023 UK NSC evidence map,[15] we do not anticipate that any meta-analyses will be undertaken. A narrative synthesis of results will be presented, structured by key question, using the UK NSC Report template. This will involve the use of text and tables to summarise data. Where appropriate, graphical representations (e.g. receiver operating characteristic [ROC] space plots) may also be used. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed.

TIMETABLE

Milestone	Date
Start	August 2024
Protocol development	September 2024
Protocol sign-off	Week beginning 30th September
Draft report to UK NSC Evidence Team	7th March
Progress report to NIHR	16th March
Receipt of comments from UK NSC Evidence Team	21st March
Updated draft report to UK NSC Evidence Team	16th April
Final report to NIHR	30th April
Fetal, maternal and child health (FMCH) reference group meeting	30th April
Provider responding to the feedback from FMCH	Updated version to be ready 1 or 2 weeks after receiving feedback
Public consultation	Usually 3-months but can be less
UK NSC meeting	Feedback from UK NSC to be sought at earliest opportunity
Supplier responding to the feedback from the UK NSC and public consultation, if required	Final document to be ready as soon as possible after the UK NSC meeting

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APPENDIX 1 Draft Embase search strategy

To be amended in consultation with the commissioner

Embase (Ovid): 1974-2024/08/14
Searched: 15.8.24

1 exp Metachromatic leukodystrophy/ (2505)
2 (MLD and (gene$ or ARSA or ASA or arylsulfatase or arylsulphatase or leukodystroph$ or leucodystroph$)).ti,ab,ot. (1854)
3 (Metachromatic adj2 (leukoencephal$ or leucoencephal$ or leukodystroph$ or leucodystroph$)).ti,ab,ot,kw,hw. (2736)
4 (("Arylsulfatase A" or "arylsulphatase A" or "epididymis secretory sperm binding protein") adj2 deficien$).ti,ab,ot,kw,hw. (355)
5 Greenfield$ Disease.ti,ab,ot,kw,hw. (0)
6 (Cerebroside adj2 (Sulfatase or Sulphatase) adj2 Deficien$).ti,ab,ot,kw,hw. (45)
7 (cerebroside adj2 (sulfate or sulphate) adj2 storage disease).ti,ab,ot,kw,hw. (0)
8 ((ASA or ESSPB or ARSA) adj2 Deficien$).ti,ab,ot,kw,hw. (195)
9 Cerebroside Deficien$.ti,ab,ot,kw,hw. (0)
10 ((diffuse or metachromatic) adj3 (Cerebral or brain) adj3 sclerosis).ti,ab,ot,kw,hw. (29)
11 ((sulfatide or sulphatide) adj2 lipidosis).ti,ab,ot,kw,hw. (11)
12 (mckusick-25010 or mckusick25010).ti,ab,ot,kw,hw. (0)
13 (sulfatidosis or sulphatidosis).ti,ab,ot,kw. (18)
14 or/1-13 (3840)
15 animal/ (1675803)
16 animal experiment/ (3199712)
17 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (7925316)
18 or/15-17 (7925316)
19 exp human/ (26990973)
20 human experiment/ (669241)
21 or/19-20 (26993767)
22 18 not (18 and 21) (5897018)
23 14 not 22 (3473)
24 limit 23 to yr="2012 -Current" (1784)