SWEDISH AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT AND ASSESSMENT OF SOCIAL SERVICES

English Summary

Newborn screening for Metachromatic Leukodystrophy

A systematic Review

October 2025. The full report in Swedish (www.sbu/xxx)

Main message

There is insufficient evidence to evaluate the accuracy of a screening test for metachromatic leukodystrophy (MLD) in newborns. Likewise, there is insufficient evidence to determine the efficacy of gene therapy using autologous stem cells to treat MLD.

Results

Based on the systematic search conducted in December 2024, we found:

- A screening test for MLD appears able to detect most MLD cases within a newborn population. However, more studies are required to evaluate its accuracy.
- There is insufficient evidence to evaluate the effectiveness of gene therapy using autologous stem cells on motor skills, cognitive or social function in MLD patients, as only one relevant study was included.

Aim and background

The aim of this systematic review was to evaluate the scientific literature regarding MLD screening tests for newborns and gene therapy for MLD patients, to support the National Board of Health and Welfare in their development of newborn screening programs.
MLD is a very rare inherited disorder that affects the central nervous system, leading to loss of cognitive and motor skills and eventually death. There are four different forms of the disease: late infantile, early juvenile, late juvenile and adult form. The first two forms present at an early age and progress more rapidly (particularly the late infantile form) than the late juvenile or adult forms. The effectiveness of treatment depends on early detection, preferably already pre-symptomatic. Gene therapy has been available for pre-symptomatic late infantile and pre-symptomatic or early symptomatic early juvenile MLD for the last few years, but not for the late juvenile or adult forms of MLD. As treatment is indicated for pre-symptomatic and early forms of MLD, distinguishing between the different forms prior to symptom onset is essential, justifying the evaluation of screening. Therefore, this report also includes a description of the natural course of MLD and challenges in predicting the different forms of MLD in a potential screening scenario.

Method

We conducted a systematic review and reported it in accordance with the PRISMA statement, to answer research questions pertaining to two of the National Board of Health and Welfare´s criteria for newborn screening programs. These questions were included in the systematic review (see PICO and PIRO below). Additionally, we presented a background on predicting the different forms of MLD based on experts included in the project and relevant literature identified in the search.

Inclusion criteria

PIRO
Population: Newborn children

Index test: Screening test (relevant to Swedish conditions) using dried blood spots in a two- or three-tier screening strategy; sulfatide levels followed by ARSA enzyme activity, with or without gene sequencing
Reference test: Clinical diagnosis, including confirmatory gene sequencing
Outcome: Diagnostic accuracy
Study design: Systematic reviews or quantitative primary studies

PICO
Population: Children with presumed late infantile or early juvenile MLD (in studies with mixed populations, only participants where forms differentiation was possible were included)
Intervention: Hematopoietic stem cell transplantation with gene therapy (HSCT-GT) or allogenic hematopoietic stem cell transplantation (HSCT)
Control: No intervention or other intervention aimed at treating the disease
Outcome: Mortality, motor skills, cognitive function and social function
Study design: Prospective or retrospective controlled studies

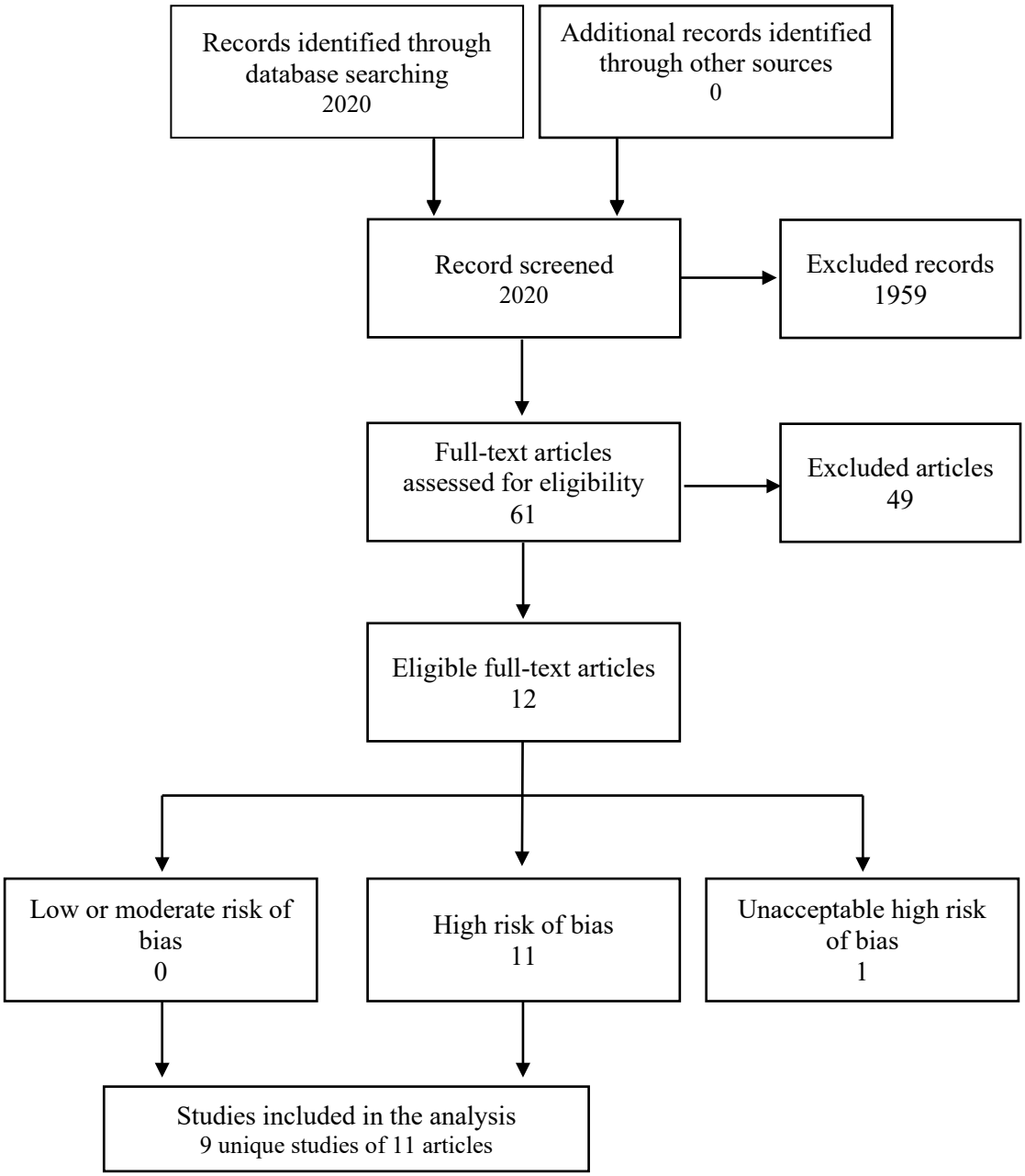
Language: English and Scandinavian languages
Databases searched: Cochrane Library (Wiley), Embase (Elsevier) and Medline (OvidSP), from 1990 to December 2024

Result

We identified three studies concerning screening tests, one study (with three publications) on HSCT-GT, and six studies on allogenic HSCT, one of which was excluded due to unacceptably high risk of bias (see Figure 1 for study flowchart).

No data synthesis or certainty of evidence rating was performed due to the small number of studies and large heterogeneity among included studies. We judge therefore that there is insufficient evidence to determine whether the screening tests or treatment are effective. However, a search for study protocols identified several ongoing studies that may be valuable for this topic further on.

Figure 1 Flow diagram of study selection.


Records identified through database searching
2020
Additional records identified through other sources
0
Record screened
2020
Excluded records
1959
Full-text articles assessed for eligibility
61
Excluded articles
49
Eligible full-text articles
12
Low or moderate risk of bias
0
High risk of bias
11
Unacceptable high risk of bias
1
Studies included in the analysis
9 unique studies of 11 articles

Discussion

This report summarizes the evidence regarding newborn screening for MLD and its implications. The paucity of research is to be expected in a field where the disease is rare, and newborn screening for MLD is only fully implemented in one country but under consideration in others. Other systematic reviews of HCST-GT found similar results to those presented in this report. The challenge of accurately distinguishing between MLD forms in a newborn screening context must be considered when evaluating the implementation of a potential screening program.

Conflict of Interest

In accordance with SBU's requirements, the experts and scientific reviewers participating in this project have submitted statements about conflicts of interest. These documents are available at SBU's secretariat. SBU has determined that the conditions described in the submissions are compatible with SBU's requirements for objectivity and impartiality.

Appendices

- Search strategies (link)
- Excluded references (link)
- Risk of Bias in included studies (link)
- Characteristics of included studies (link)