Metachromatic Leukodystrophy 2023

ICER SNAPSHOT

Reviewed for accuracy by: The MLD Foundation

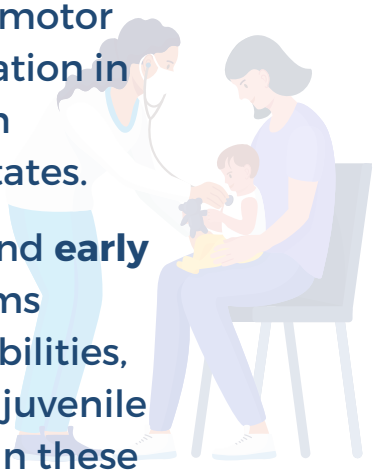
The ICER Snapshot is a summary designed to help patients and the broader community learn about the key results and recommendations from ICER's 2023 Final Evidence Report on a gene therapy for metachromatic leukodystrophy.

The information included is up to date as of October 2023. New information about these therapies may become available, but is not captured here.

Let's Take a Look

What is Metachromatic Leukodystrophy?

Metachromatic leukodystrophy (MLD) is a **rare, fatal genetic disorder** that is characterized by the progressive loss of motor and cognitive function. The disorder is caused by a mutation in the ARSA gene that leads to nerve damage. There are an estimated 2,500 people living with MLD in the United States.



There are different subtypes of MLD. The **late infantile** and **early juvenile** are the most aggressive forms of MLD. Symptoms include loss of the ability to walk, swallow, learning disabilities, and behavioral issues. Untreated late infantile and early juvenile patients die within 8 and 10-20 years, respectively. Within these subtypes, patients can be considered **presymptomatic** (prior to onset of symptoms) or **early symptomatic** (showing early signs of disease such as reduced quality of motor function).

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Impact on Patients and Families

What ICER Learned from the Community

Initial diagnosis is challenging when parents and clinicians don't recognize early symptoms

Delayed diagnosis affects child's eligibility for treatment and clinical trials

Parents experience a physical toll from lifting their children who have lost motor function

Cognitive and mobility difficulties result in the need for individualized education plans and additional help at school

Families often need to modify their homes and buy wheelchair vans to accommodate the child's disabilities

Families face a large financial impact of MLD, raising equity concerns for those with lower incomes or no insurance

Navigating insurance coverage is time-consuming and delays in care could worsen outcomes for children

Newborn screening is a key focus of advocacy to identify MLD before symptom onset for faster access to therapy

Treatment of Focus in ICER's Review

GENE THERAPY

Atidarsagene autotemcel or **"arsa-cel"**, made by Orchard Therapeutics, is a therapy that patients only take once.

*Arsa-cel is under FDA review as of October 2023.

HOW IT WORKS

Introduces a **working copy of the ARSA gene** into a patient's stem cells that helps preserve cognitive and motor function. Chemotherapy and bone marrow conditioning are part of the treatment.

MLD SUBTYPES INCLUDED IN CLINICAL TRIALS

Late Infantile	Early Juvenile	Trial Exclusion
18 patients Symptoms start before 30 months old	**17 patients** Symptoms start between 30 months to 6 years old	Children with MLD who went through stem cell transplant or still had cells from original donor

What Did Clinical Trials Show?

35 patients* treated with **arsa-cel** followed for up to **11 years**

*compared to untreated children

- **INCREASED** survival
- **PRESERVED** motor function
- **PRESERVED** cognitive function

These represent some, but not all outcomes that were measured in the clinical trials. In addition, clinical trials showed greater benefit for children who did not yet show symptoms for MLD.

Safety of Arsa-Cel

Serious adverse events such as **febrile neutropenia** and **stomatitis** were reported in the trials, mainly linked to the bone marrow conditioning required before receiving arsa-cel. This gene therapy also carries a risk of death. The **long-term risks** of this gene therapy in the real world is still **uncertain**.

ICER's report findings are NOT recommendations that support the use of this gene therapy. Patients and families should always talk with their doctors to make shared decisions about treatment for MLD.

What We Still Don't Know

- How the therapies work for patients beyond the first decade
- How well the gene therapies work outside of clinical trials
- What level of ARSA is required to stop progression and how this ARSA level is associated with other clinical outcomes
- For older children (early juvenile) showing early symptoms, if the therapy actually quickens the progression of physical and cognitive decline before the patient stabilizes

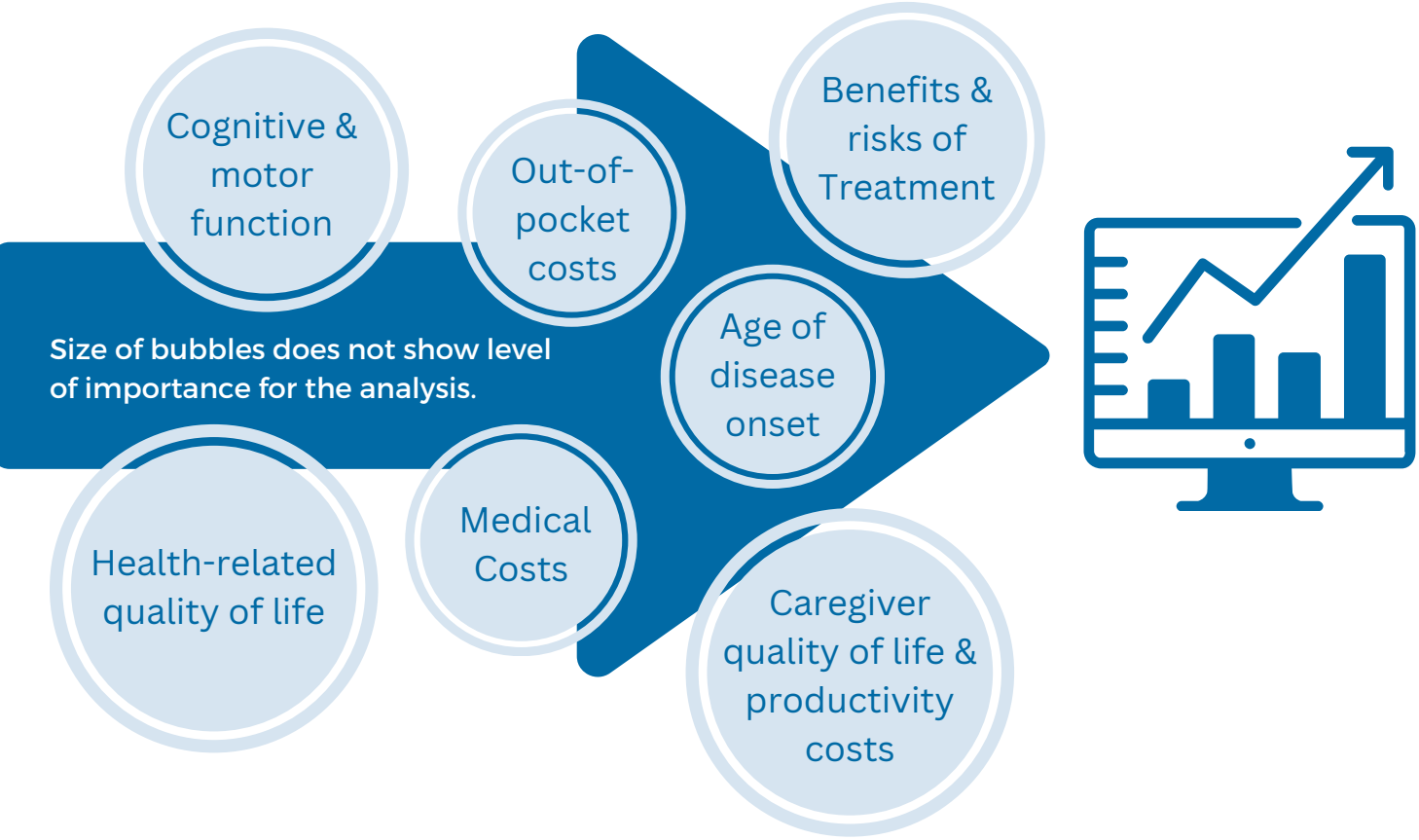
How Did ICER Calculate a Fair Price?

Using economic modeling, we calculated the cost-effectiveness of arsa-cel based on how well it preserved cognitive and motor function, compared to usual care. See below for what types of information ICER considered to calculate a fair price range for this gene therapy.

Population

This analysis included patients with **late infantile MLD** (presymptomatic) or **early juvenile MLD** (who were either presymptomatic or early symptomatic)

Factors Included in ICER's Economic Analysis



Fair Price Range for Arsa-cel

$2.3 - $3.9 MILLION

A fair price is how much a treatment should cost based on how well it works for patients. Our economic analysis concluded that the fair-price range for arsa-cel is between $2.3 and $3.9 million. This price is for a one-time treatment.

Key Policy Recommendations

The Policy Roundtable at the ICER public meeting informed several policy recommendations for pricing, access, guidelines, and future research in MLD. A few key recommendations are summarized below.

1 Patient organizations have a vital role to play to promote greater visibility for the diagnosis and treatment of MLD, including newborn screening.

Now that there is an effective treatment on the horizon, the MLD patient community should continue to work with other stakeholders to implement newborn screening for the early diagnosis of MLD. Patient groups also have an ongoing responsibility to educate families about the potential risks and benefits of new therapies, particularly for the early symptomatic early juvenile MLD population where there is a risk of achieving decreased health after treatment.

2 Patient groups have a powerful voice to create significant pressure for fair pricing and appropriate insurance coverage across all parts of the health system.

Working with insurance plans and clinical societies, patient organizations can help lead the work to improve access to treatments and hold drug makers accountable to fair pricing.

3 Payers (public and private health insurance plans) should provide insurance coverage including transportation and housing to ensure equal access to treatment.

Given that most patients with MLD will need to travel to obtain treatment with arsa-cel, payers should provide wraparound coverage including transportation and housing. All patients should have the fundamental right to fair access that is not undermined by geographical or income barriers.

4 Payers who serve a significant population of underserved patients should minimize financial barriers to treatment with arsa-cel and provide an adequate network of providers with the needed clinical expertise to support patients from diverse communities.

Since there is a higher incidence of MLD in the Navajo and Alaska Native groups, the Indian Health Service should be prepared to establish Centers of Excellence or referral pathways to ensure their populations receive timely care. All payers should ensure that their networks include Centers of Excellence or efficient ways for patients/families to seek treatment at out-of-network Centers of Excellence and across state lines.

5 No step therapy (when payers require taking another treatment first) is appropriate for treatment of presymptomatic or early-onset forms of MLD.

Since arsa-cel is most effective before symptoms are noted and progression of disease is often rapid after symptom onset, it is not appropriate for payers to require treatment with stem cell transplant prior to treatment with arsa-cel.

Impact of Patient Engagement

Community input helped inform ICER's understanding of **family preferences for receiving gene therapy**.

Public comment on our draft report led ICER to **adjust our evidence rating to reflect greater benefit for patients** in the early symptomatic early juvenile group.

Patient and caregiver testimony at the public meeting helped shape ICER's recommendations for policy makers to provide **equitable access to arsa-cel**.

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit organization that does research on how well new treatments work and what a fair price should be. Patients and families should always talk with their doctor to make shared decisions about the best treatment option for them.

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