Atidarsagene Autotemcel for Metachromatic Leukodystrophy: Final Policy Recommendations

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Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the September 29, 2023 CTAF public meeting on the use of atidarsagene autotemcel for the treatment of metachromatic leukodystrophy. At the meeting, ICER presented the findings of its revised report on these treatments and the CTAF voting council deliberated on key questions related to their comparative clinical effectiveness, potential other benefits and contextual considerations, and long-term value for money at current prices. Following the votes, ICER convened a Policy Roundtable of two patient representatives, two clinical experts, two payers, and one representative from a pharmaceutical manufacturer to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed here, and a recording of the voting portion of the meeting can be accessed here. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found here.

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

All Stakeholders

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that effective new treatment options for patients with late infantile (LI) and early juvenile (EJ) metachromatic leukodystrophy (MLD) are introduced in a way that will help reduce health inequities.

The early onset forms (LI and EJ) of MLD are rapidly progressive and fatal. The disorder is rare, occurring in approximately 1 in 100,000 persons in the US.[1] Higher rates of disease occur in Navajos and Alaska Natives.[1] Because the disorder is rare, there can be delays in diagnosis, and children typically do not get diagnosed until they become symptomatic unless they have an older affected sibling. Until now, there has not been an effective treatment for this disease, and treatment consisted of supportive care only.

With the advent of an effective treatment on the horizon that is most effective in the pre-symptomatic and early symptomatic stages, access to newborn screening will become a critical step to facilitate rapid and equitable diagnosis and treatment. Delays in implementation of newborn screening for MLD will delay or deny access to treatment if children are diagnosed too late to be eligible for treatment. Thus, coordination of newborn screening will be of paramount importance as soon as arsa-cel receives FDA approval. Unfortunately, there are complex challenges in moving rapidly to broad adoption of a new newborn screening test across the US, as screening panels are decided upon at the state level. Another challenge that should be anticipated is that newborn screening is likely to turn up new genotypic variants of uncertain significance that will lead to much uncertainty about appropriate treatment and that will not fit easily within insurance coverage criteria built upon current epidemiologic data.

Finally, since MLD is a rare disease, only a few specialized centers are likely to have the expertise to offer treatment. Thus, children and their families may face geographic and financial barriers beyond the cost of arsa-cel treatment that may widen disparities unless systematic steps are taken by insurers and others.

To address these concerns:

<u>Policymakers managing newborn screening should take the following actions</u>:

- Policymakers and leaders who manage state and federal procedures governing universal newborn screening should prepare to be able to offer testing for MLD as soon as the test is available. This will require that officials at the Department of Health and Human Services evaluate and add the MLD screen to the Recommended Uniform Screening Panel (RUSP) in a timely manner. In addition, state health leaders should anticipate the addition of MLD to the RUSP and be primed to offer a rapid review and approval process for adding MLD screening to state panels.

- Given the higher prevalence of MLD in the Navajo and Alaska Native populations, policymakers should ensure that tribal health services have adequate funding and other resources to offer screening and expeditious access to treatment, whether within the Indian Health Service or externally.

<u>Payers and plan sponsors should take the following actions:</u>

- State Medicaid payers should ensure that their specialist referral networks are adequate to ensure timely access to confirmatory testing for MLD and to treatment with arsa-cel. For a rare disease such as MLD, it will be particularly important for patients to have access to Centers of Excellence, such as Leukodystrophy Care Network Certified Centers, which will have the most experience treating MLD patients and are most likely to offer arsa-cel therapy.

- 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 to ensure equal access to treatment. Geographical and income constraints should not undermine the tenets of fair access to which all patients have a fundamental right.[2]

- Employers and other plan sponsors should avail themselves of re-insurance and financial protection programs offered by payers (e.g., EMBARC from Cigna[3]) to help manage the high cost of arsa-cel. Plan sponsors should not abandon coverage of gene therapies or exclude coverage for MLD specifically.

Clinicians and clinical specialty societies should take the following actions:

- Ensure that Centers of Excellence clinicians are accredited with public and private insurance plans across multiple state lines to allow patients to travel to centers with the expertise and treatment options appropriate for their situation.

- Newborn screening will generate new findings of genetic variants of unknown significance, and therefore clinical societies should foster sharing of data in a readily accessible manner (e.g., searchable online database or website) and develop guidelines to help clinicians and families navigate the uncertainty in whether newborns with uncertain findings should receive immediate treatment with arsa-cel or not.

Payers

Recommendation 1

In the context of a rapidly progressive disease such as MLD, when a treatment has a high likelihood of being approved by the FDA, payers should be evaluating evidence and preparing policies in advance to avoid a new-to-market block on insurance coverage.

Many payers now institute "new-to-market" policies that block routine insurance coverage for new drugs for up to 180 days after FDA approval. Although in principle these blocks can be justified to allow an insurer adequate time to review the clinical evidence, discuss with clinical experts, and prepare special delivery or other policies, in practice many insurers now place new-to-market blocks on virtually any new specialty drug. In the case of arsa-cel for MLD, the evidence of transformative benefit is strong, providing assurance that FDA approval is extremely likely. Given the rapidly progressive nature of the condition and the importance of early treatment upon diagnosis, payers should recognize their responsibility to act now to ensure that coverage is ready "on day one" of FDA approval, currently anticipated in March 2024. This preparation is facilitated when manufacturers engage with payers prior to approval of their products to facilitate

establishment of payment policies, much as Orchard Therapeutics has reported doing in advance of approval of arsa-cel.

Recommendation 2

Payers who serve a significant population of underserved patients should ensure that they minimize any financial barrier 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 either establish Centers of Excellence or to establish referral pathways to other Centers of Excellence (e.g., Leukodystrophy Care Network Certified Centers) to ensure their populations receive timely care. Additionally, given that there are likely to be few centers with the expertise to offer arsa-cel treatment, all payers should ensure that their networks either include Centers of Excellence or there are efficient mechanisms for patients and families to seek treatment at out-of-network Centers of Excellence. In particular, if single case agreements are necessary for out-of-network care, these contracts would ideally be set up proactively rather than developed as needed for individual patients, since delays in care for MLD patients can affect eligibility for treatment and impact disease-related complications.

Recommendation 3

Payers should cover fertility preservation in concert with coverage of gene therapies.

Patient stakeholders noted that future fertility is a consideration in management. There are many complex issues regarding fertility (e.g., prepubescent patients, ongoing storage). Payers should be aware that this will be discussed with patients and must be pro-active and transparent about what will be covered.

Coverage Criteria: General

Given the high cost of arsa-cel and the uncertain long-term outcomes, it is reasonable for payers to use prior authorization as a component of coverage. Prior authorization criteria for arsa-cel should be based on clinical evidence and input from clinical experts and patient groups. The process for authorization should also be clear, accessible, efficient, and timely for providers. Perspectives on specific elements of cost sharing and coverage criteria within insurance coverage policies are discussed below. Relevant Fair Access Design Criteria set out in ICER's previous work are included.

Drug-Specific Coverage Criteria: Arsa-cel

Although MLD is an ultra-rare disease, treatment with arsa-cel is likely to have a very high one-time cost and thus payers will develop prior authorization criteria and consider other limits on utilization.

None of these limits, however, should undermine the tenets of fair access to which all patients have a fundamental right.[2] To explore the appropriate application of evidence to coverage policy, and to reflect the views of patient experts and clinicians on specific ways that payers might appropriately use coverage policy to manage resources prudently, we present the following perspectives on specific elements of cost sharing and coverage criteria for arsa-cel.

Coverage Criteria

- **Diagnosis:** Diagnosis of MLD is based on a combination of clinical presentation, biochemical testing (e.g., arylsulfatase A enzyme activity, urine sulfatide levels), brain MRI, and/or genetic testing for mutations in the ARSA gene. Diagnosis of presymptomatic disease will either be through testing of siblings of a previously affected and diagnosed child or through newborn screening. Widespread newborn screening will detect variants of uncertain significance; these variants may lead to difficult decisions about appropriate treatment and insurance coverage, since it is not known whether some genetic mutations may lead to a later onset or possibly milder form of the disease for which the harms of gene therapy may outweigh any benefits. If payers require genetic testing to establish diagnosis, they should have mechanisms to ensure that there are no delays in obtaining genetic testing and results, and to not require repeated documentation of genetic testing results.

- **Age:** It is unclear whether the FDA will specify an age or weight range in its approved indication for arsa-cel, so payers may be left to decide whether to include some threshold in coverage criteria. Clinical experts advised that there may be a minimum weight (e.g., 5-7 kg) to undergo treatment safely, but if treatment decisions are reserved for experts at Centers of Excellence it may be reasonable for payers to leave age and weight criteria to the discretion of these experts. If payers do set age or weight criteria based on the clinical spectrum of patients in the pivotal trial, they should ensure that clinicians have efficient mechanisms for seeking coverage exceptions for patients who are near whatever thresholds are set.

- **Clinical eligibility**: Treatment with arsa-cel will likely be restricted to the populations included in the clinical trials: presymptomatic late-infantile, presymptomatic early juvenile, and early symptomatic early juvenile MLD. There is no current evidence that children with late juvenile or adult MLD should be treated with arsa-cel; ongoing trials will provide data on the efficacy and safety of arsa-cel treatment for the late juvenile population.

    - Payers need to consider whether to establish criteria for the diagnosis of late-infantile or early juvenile MLD, particularly for presymptomatic patients. According to clinical experts and clinical studies, there is high concordance between genotype and phenotype, particularly among siblings,[4] and thus payers will need to decide

whether documentation of a genotype known to be associated with late-infantile or early juvenile MLD is necessary or whether clinician attestation will suffice. In addition, as noted earlier, there will be new variants of uncertain significance that will emerge with newborn screening, and payers need to be ready to either quickly update their criteria when new evidence becomes available or rely on clinician attestation for diagnosis.

    - Payers will also need to consider whether to use a specific definition of early symptomatic early juvenile MLD. Clinical experts advised that it is reasonable to apply the clinical trial criteria of GMFC-MLD 0-1 and IQ≥85; however, payers will need to have a process to consider exceptions for impairments due to non-MLD comorbidities (e.g., motor impairments that may be due to comorbid cerebral palsy rather than MLD) or for patients close to the IQ cutoff.

- **Exclusion criteria**: In the clinical trials, children who received treatment with hematopoietic stem cell transplant (HSCT) within the last six months and with residual cells of donor origin were excluded from the trial. Given that treatment with arsa-cel includes autologous HSCT, it is reasonable for payers to adopt this exclusion for coverage.

- **Dose:** The dose of arsa-cel is weight-based and should follow dosing in the clinical trials.

- **Duration of coverage and renewal criteria**: This is a one-time treatment; there is no evidence that repeat treatments are indicated.

- **Provider restrictions**: Clinical experts agreed that treatment should be done at specialized centers. Because MLD is a rare disease, specialty clinicians are better suited to identify patients who are most likely to benefit, provide sufficient information for caregivers to make a well-informed decision about treatment, and monitor for response and side effects.

Step Therapy

No step therapy is appropriate for treatment of the early-onset forms of MLD.

For the early-onset forms of MLD, clinical experts and clinical practice guidelines agreed that HSCT has inferior clinical outcomes compared with arsa-cel. Since arsa-cel is most effective before symptoms are noted and progression of disease is often rapid after onset of symptoms, it is not appropriate for payers to require evaluation for or treatment with HSCT in the late infantile and early juvenile forms of HSCT prior to treatment with arsa-cel.

Manufacturers

Recommendation 1

Manufacturers should provide transparent, explicit justification for their pricing. To foster affordability and good access for all patients, manufacturers should align prices with the patient-centered therapeutic value of their treatments.

Drug prices that are set well beyond the cost-effective range cause not only financial toxicity for patients and families using the treatments, but also contribute to general health care cost growth that pushes families out of the insurance pool, and that causes others to ration their own care in ways that can be harmful.

Recommendation 2

Manufacturers should actively engage with independent value assessment efforts to allow public dialogue on access and fair pricing with broad input from patients and other stakeholders. Orchard Therapeutics has set a good example for other developers of transformative gene therapies.

Although more manufacturers are engaging in developing and sharing cost-effectiveness models to assess the value of their new drugs, industry-sponsored cost-effectiveness analyses show a bias towards reporting lower incremental cost-effectiveness ratios.[5] Thus, independent value assessments are important to inform pricing and insurance coverage policies. Manufacturers should follow the example of Orchard Therapeutics and engage with organizations that provide independent value assessments to seek a fair launch price.

Recommendation 3

Although many high-impact single and short-term therapies are good candidates for outcomes-based contracts, arsa-cel is not an ideal candidate given the very small patient population and the difficulty in framing reasonable outcome measures indicative of treatment success.

Outcomes-based contracts are increasingly being used for high-cost treatments, and are often considered for transformative gene therapies. However, use of outcomes-based contracts requires clear and achievable benchmarks. In the case of arsa-cel, it is possible that the manufacturer will pursue agreements based on engraftment. However, all patients in the clinical trials achieved full engraftment; thus, it would not be an appropriate outcome on which to base payment. Furthermore, in children with MLD treated with arsa-cel, it is not yet clear at which time points it is reasonable to measure clinically meaningful outcomes.

Patient Organizations

Recommendation 1

Patient organizations have a vital role to play to promote greater visibility for the diagnosis and treatment of MLD, including newborn screening. In addition, patient groups have a powerful voice and should apply it to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system.

The MLD patient community has been very active in the development of newborn screening and should continue to work with other stakeholders to implement newborn screening to facilitate the early diagnosis of MLD, now that there is an effective treatment on the horizon. Patient groups also have an ongoing responsibility to educate families about the potential risks and benefits of new therapies, particularly for the early symptomatic EJ-MLD population where there is a risk of stabilization in a worse state than prior to treatment. Furthermore, patient groups should work with other stakeholders to develop and disseminate evidence-based, balanced materials that are accessible to all patients, including those with low health literacy. Finally, patient groups should accept responsibility to publicly promote access and fair pricing of new therapies.

Researchers

Recommendation 1

With newborn screening and gene therapy on the horizon, diagnostic accuracy will be critical. An important area of focus for future research should be to continue to develop and refine biomarkers that can help predict disease type and severity.

Currently, the benefits of arsa-cel treatment appear greatest in the presymptomatic phase of the late-infantile and early juvenile forms of MLD. Therefore, early and accurate diagnosis is critical. Although there are known genotype-phenotype correlations, newborn screening will uncover new variants where type and severity of MLD will be unknown. This uncertainty will prevent some children from receiving treatment in the presymptomatic stage. While there are some data that levels of ARSA enzyme can be predictive of phenotype, continued research in this area should be a priority for researchers and funding agencies to clarify and refine this relationship such that clinicians will be able use biomarkers to help make treatment decisions. This has been successfully done in other diseases such as globoid cell leukodystrophy and would seem to be a reasonable goal for MLD as well.

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Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the September 29, 2023 Public meeting of CTAF.

Appendix Table 1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants*	
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Sarah Emond, MPP, President-Elect, ICER	**Steven Pearson, MD, MSc,** President, ICER
Shahariar Mohammed Fahim, PhD, Research Lead, Evidence Synthesis, ICER	**Finn Raymond, BS**, Research Assistant, ICER
Kelsey Gosselin, MA, Program Manager, ICER	**Marina Richardson, PhD, MSc,** Senior Health Economist, ICER
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*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 2. CTAF Panel Member Participants and COI Disclosures

Participating Members of CTAF and New England CEPAC*	
Ralph Brindis, MD, MPH, MACC, FSCAI, FAHA, Clinical Professor of Medicine, UCSF	**Donald Kreis, JD,†** Consumer Advocate, New Hampshire Office of the Consumer Advocate
Robert Collyar, Patient Advocate, Breast Cancer; Board Member, Breast Cancer Action; Co-Founder, Clinical Trials Information Project	**Sei Lee, MD, MAS,** Associate Professor of Medicine, UCSF
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*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess

of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.
†Members of NE CEPAC

Appendix Table 3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Laura Adang, MD, PhD, Assistant Professor of Neurology, Children's Hospital of Philadelphia	Dr. Adang is a consultant to Takeda Pharmaceuticals and Orchard Therapeutics. She is also a co-investigator on a Takeda clinical trial.
Francesca Fumagalli, MD, PhD, Neurologist, Pediatric Immunohematology Unit and Department of Neurology, IRCCS San Raffaele Hospital, Milan	Dr. Fumagalli is a sub investigator of clinical trials NCT01560182 and NCT03392987 and PI of clinical trial NCT04283227 using OTL-200 sponsored by Orchard Therapeutics. Dr. Fumagalli has received less than $5,000 in honoraria from Orchard Therapeutics and Takeda.
Stephen Jung, PharmD, Principal Pharmacist, Blue Shield of California	Stephen is a full-time employee of Blue California.
Maria Kefalas, PhD, Founder, Cure MLD; Professor, Saint Joseph's University	Cure MLD has received grants from Bluebird Bio, Homology Medicines, Orchard Therapeutics, Takeda Pharmaceuticals, and Passage Bio, Inc.
Julia Mahler, PharmD, Clinical Pharmacist, IPD Analytics	Julia is a full-time employee of IPD Analytics.
Paul Orchard, MD, Professor of Pediatric Blood and Marrow Transplantation and Cellular Therapy, University of Minnesota	Dr. Orchard's team offers expanded access to OLT-200 in association with Orchard Therapeutics for specific patients. He has received less than $5,000 in honoraria or consultancies from Orchard Therapeutics.
Francis Pang, MBA, SVP Global Market Access and International Geographic Expansion, Orchard Therapeutics	Francis is a full-time employee of Orchard Therapeutics.
Teryn Suhr, RN, Executive Director & Co-Founder, MLD Foundation	The MLD Foundation has received sponsorships from various biopharma companies for their annual family conference.