FROM CLUES TO CARE: IMPROVING RECOGNITION AND TREATMENT OF ALPHA-MANNOSIDOSIS

ANNENBERG CENTER FOR HEALTH SCIENCES
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What is Alpha-Mannosidosis (AM)?

- AM is an inherited metabolic disorder caused by faulty or absent alpha-mannosidase in lysosomes → accumulation of mannose-containing oligosaccharides → cellular dysfunction and apoptosis
  - Caused by the presence of 2 pathogenic variants in the *MAN2B1* gene[1]

- Incidence: 1 in 250,000 and 1 in 1 million live births[1]

1. Santoro L, et al. *Mol Genet Metab*. 2024;142(1):108444.

Case Vignette

Infancy	Early Childhood	Childhood	Early Adulthood

- Second child born to Palestinian parents who are first cousins
- Normal at birth

- Multiple hospital admissions between 7 and 11 mos of age for reactive airway disease
- Chest X-ray at 10 mos of age revealed findings suggestive of dysostosis multiplex
- Hepatomegaly noted at 11 mos of age
- Geneticist suspected MPS disorder and obtained urine GAGs
- Liver biopsy recommended

GAG, glycosaminoglycan; mos, months; MPS, mucopolysaccharidosis.

Case study provided by Dr. Barbara Burton and shared with permission.

Case Vignette

Infancy	**Early Childhood**	Childhood	Early Adulthood

- Parents sought a second opinion with a hepatologist
- Physical examination revealed coarse facial features, frontal bossing, and broad nasal bridge
- Liver edge 5 cm below RCM, spleen 5 cm below LCM
- Lumbar kyphosis
- Mild hypotonia
- Suspected storage disorder → referred to genetics
- Urine GAGs normal, urine oligosaccharides abnormal
- Lysosomal enzyme panel revealed deficient alpha-mannosidase activity

LCM, left costal margin; RCM, right costal margin.

Case study provided by Dr. Barbara Burton and shared with permission.

3 Phenotypic Subtypes of AM[1,2]

Characteristic	Type 1	Type 2	Type 3
Severity	Mild	Moderate	Severe
Age at clinical recognition	>10 y	≤10 y	Early infancy
Rate of progression	Very slow	Slow, ataxia at 20–30 y	Rapid, early death from primary central nervous system involvement or myopathy
Skeletal involvement	No	Yes	Yes
Prominent signs and symptoms	Hearing loss, intellectual disability, ataxia, psychiatric disorder, arthritis, autoimmune disorders	Speech delay, hearing loss, developmental delay, motor disturbances/joint laxity, characteristic facial features, infections, mild hepatosplenomegaly, hernia	Skeletal abnormalities, facial dysmorphia, profound hearing loss, hepatosplenomegaly, marked and progressive deterioration in motor and cognitive function

y, years.

1. Guffon N, et al. *Mol Genet Metab*. 2019;126(4):470-474.
2. Santoro L, et al. *Mol Genet Metab*. 2024;142(1):108444.

Genetic Testing – ACMG Guidelines[1]

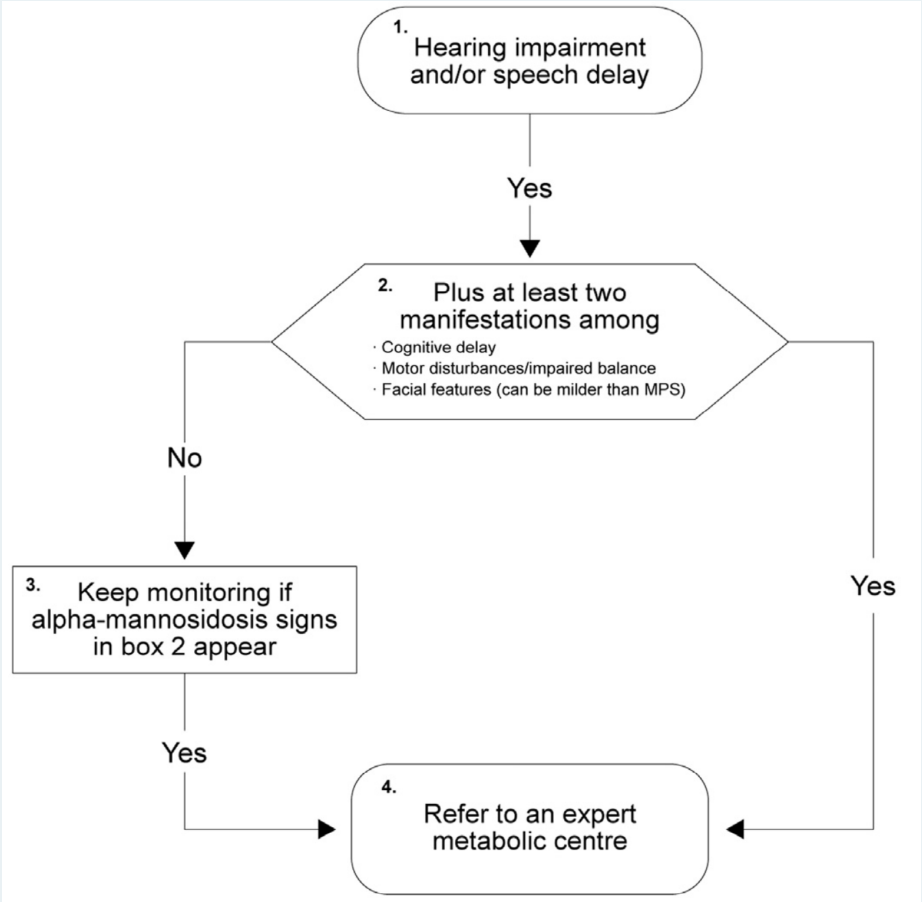
- Strongly recommend **exome sequencing** and **genome sequencing** as a first-tier or second-tier test for:
  - Patients with ≥1 congenital anomaly prior to 1 year of age
  - Patients with developmental delay/intellectual disability with onset prior to 18 years of age
- Guided by clinical judgment
- Clinician-patient/family shared decision-making often pursued after chromosomal microarray studies or focused testing

ACMG, American College of Medical Genetics and Genomics

1. Manickam K, et al. *Genet Med*. 2021;23(11):2029-2037.

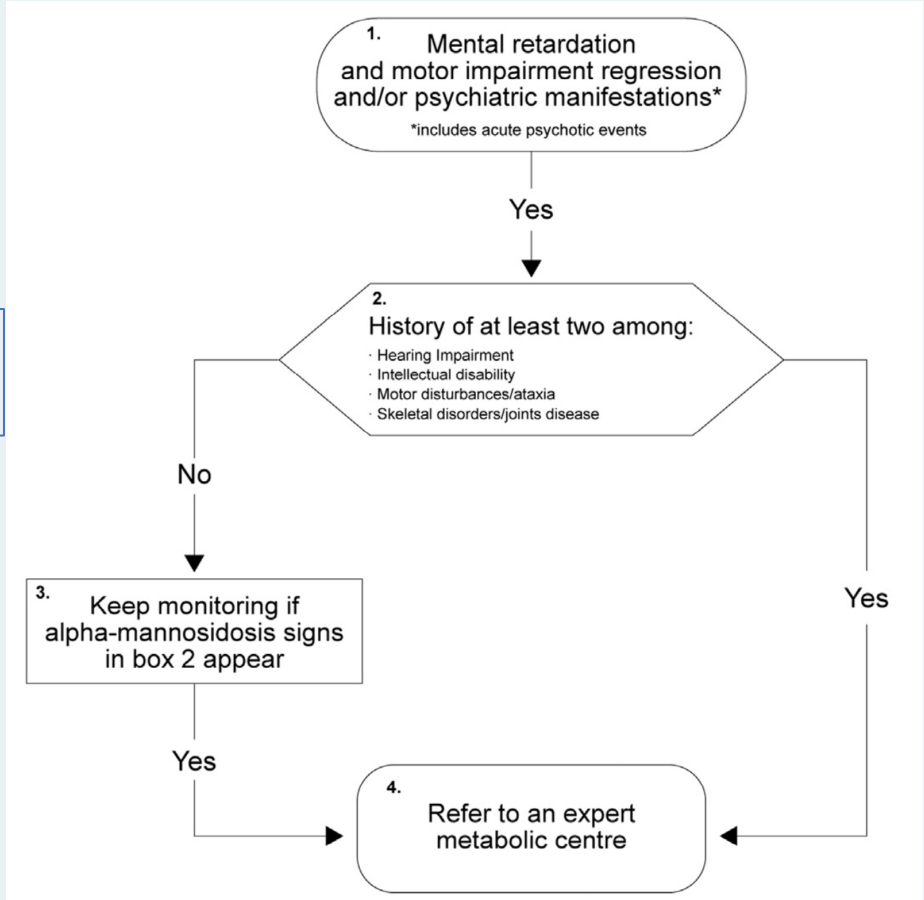
Diagnostic Algorithms for AM

Proposed algorithm for diagnosis of AM in patients **≤10 y**[1]



Diagnostic Algorithms for AM

Proposed algorithm for diagnosis of AM in patients **>10 y**[1]

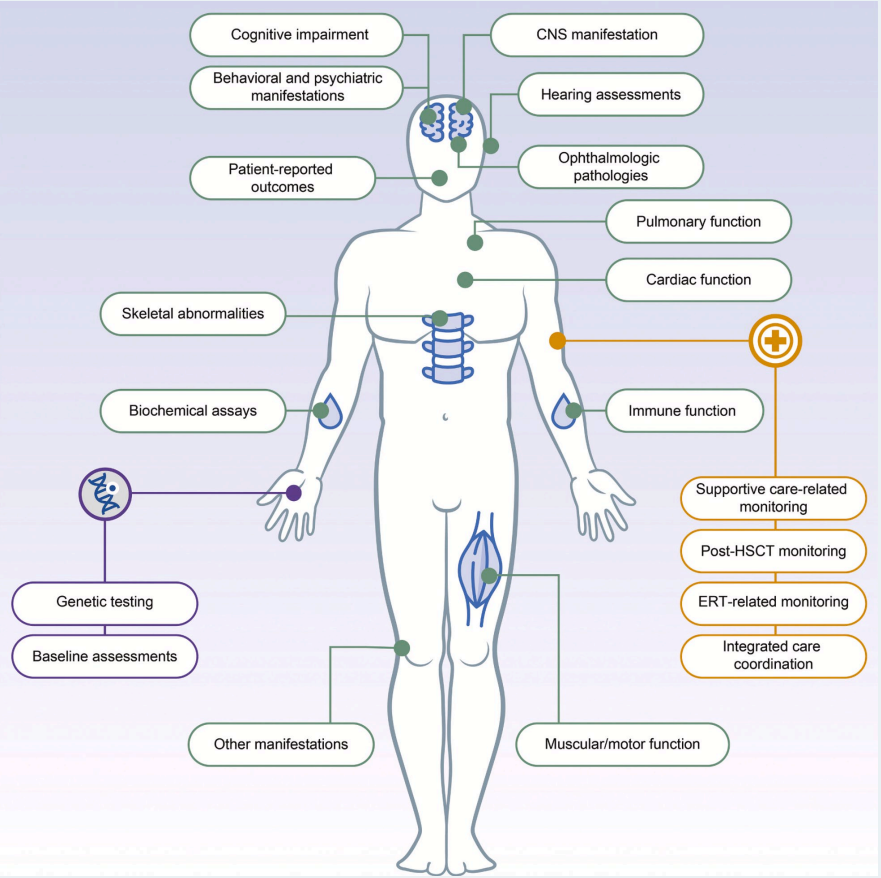


2024 Global Delphi Consensus Recommendations[1]

Key area 1:
Assessments in newly diagnosed patients

Key area 2:
Routine follow-up care

Key area 3:
Treatment-related follow-up care



2024 Global Delphi Consensus Recommendations[1]

Genetic Testing
Genetic testing should be incorporated for a confirmatory diagnosis of AM
A genetic counselor should be consulted to assess relatives at risk once a diagnosis is established and 2 *MAN2B1* variants are identified in a patient with AM

2024 Global Delphi Consensus Recommendations[1]

Baseline Assessments (Conducted at follow-up visit or close to diagnosis[a])

- Physical examination with growth parameters/clinical examination
- Genetic testing, if not done at diagnosis
- Patient/family history
- Audiology testing
- Laboratory assessments (biochemical, immune workup, plasma oligosaccharides)
- Neurological testing
- Abdominal examination
- Skeletal survey and orthopedic assessment consultation
- Cognitive/neurocognitive testing
- Motor function (physiotherapeutic)
- Quality of life assessments
- Ophthalmology examination
- Pulmonary function
- Cardiac function

Additional evaluations should be based on disease presentation at diagnosis, and examination findings; they should be individualized based on disease severity and patient ability

[a]Listed in decreasing order of "importance" for pediatric patients. The order of importance according to the Global Delphi Consensus is different for newly diagnosed adults with AM.

Available Disease-Directed Treatments for AM

Enzyme Replacement Therapy (ERT)[1,2]	Hematopoietic Stem Cell Transplant (HSCT)[1]
Velmanase alfa • Only FDA-approved therapy for AM • Regarded as a standard of treatment for AM • Addresses noncentral nervous system symptoms • Well tolerated • Biochemical and functional improvements • Early initiation may lead to better clinical outcomes; should be implemented early in the disease course where possible[3]	• Used for preservation of neurocognitive function and prevention of early death in severe AM • Better outcomes achieved by performing early, before complications arise • Morbidity and mortality associated with HSCT must be balanced against benefits

Access to therapy and sites of care are challenges for patients and caregivers for both treatments

1. Ficicioglu C, et al. Alpha-Mannosidosis. 2001 [updated June 13, 2024]. GeneReviews® [Internet]. University of Washington, Seattle; 1993–2024.
2. Lamzede. Prescribing information. Chiesi USA, Inc., 2023. Accessed January 7, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761278s000lbl.pdf
3. Köse E, et al. *Eur J Med Genet*. 2024;68:104927.

ERT – Velmanase Alfa

Mechanism of Action and Indication[1]

Velmanase alfa is recombinant human lysosomal alpha-mannosidase

- Provides an exogenous source of alpha-mannosidase
  - Helps catalyze degradation of mannose-containing oligosaccharides
- Transported into lysosomes where it is thought to exert enzyme activity

Velmanase alfa is indicated for the treatment of noncentral nervous system manifestations of AM in adult and pediatric patients

1. Lamzede. Prescribing information. Chiesi USA, Inc., 2023. Accessed January 7, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761278s000lbl.pdf

ERT – Velmanase Alfa

Dosage and Administration[1]
Recommended dosage: 1 mg/kg (actual body weight)
Administered once every week as an intravenous infusion • If one or more days are missed, restart treatment as soon as possible as long as it is at least 3 days from the next scheduled dose • If within next 3 days from the next scheduled dose, give only the next dose per schedule

1. Lamzede. Prescribing information. Chiesi USA, Inc., 2023. Accessed January 7, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761278s000lbl.pdf

ERT – Velmanase Alfa

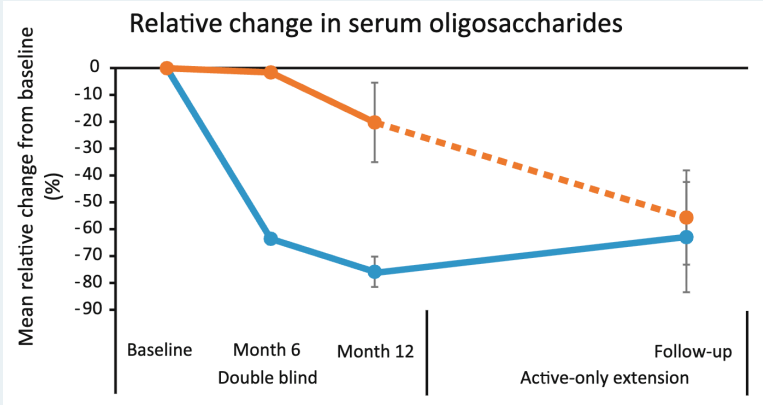
Adverse Events, Warnings, and Contraindications[1]
Most common adverse events (incidence >20%) • Hypersensitivity reactions, including anaphylaxis, pyrexia, headache, arthralgia
May cause severe infusion-associated reactions
May cause fetal harm; effective contraception during treatment and for 14 days after the last dose if discontinued required for females of reproductive potential
There are no listed contraindications to velmanase alfa

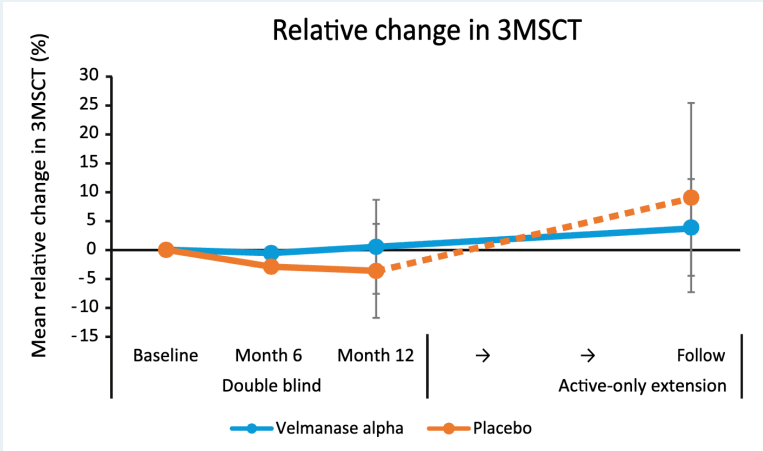
1. Lamzede. Prescribing information. Chiesi USA, Inc., 2023. Accessed January 7, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761278s000lbl.pdf

ERT – Velmanase Alfa

Pivotal Trial Data

rhLAMAN-05, Phase 3 Trial[1]
52-wk trial in 25 patients with AM, including an active treatment extension phase[a]





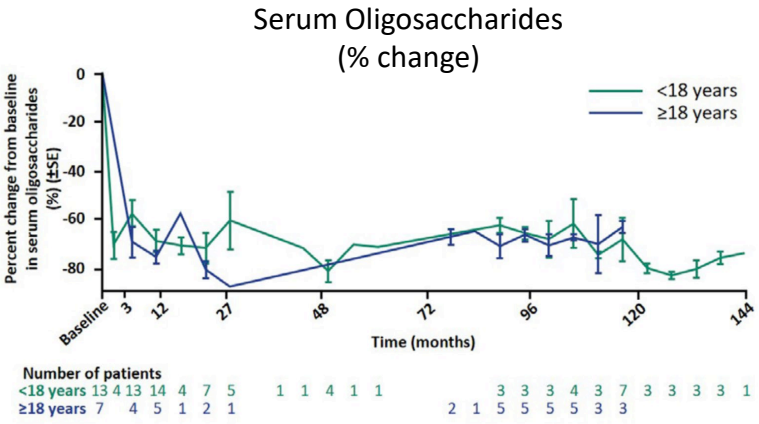
3MSCT, 3-minute stair-climb test; S-oligo, serum oligosaccharide.

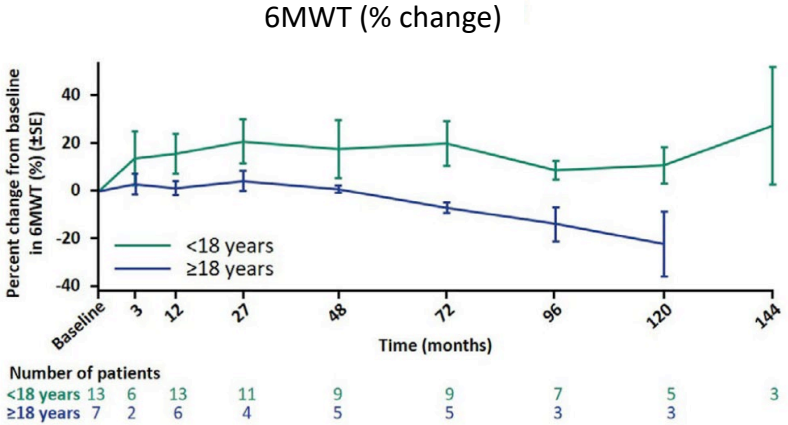
[a]Active treatment extension phase indicates outcomes in 23 patients who continued receiving velmanase alfa and were evaluated at the last observation; patients who received active treatment from the beginning of the trial received active treatment for 24–36 mos; patients who switched to active treatment from the placebo group received 12-–18 mos of treatment in the active treatment extension phase.

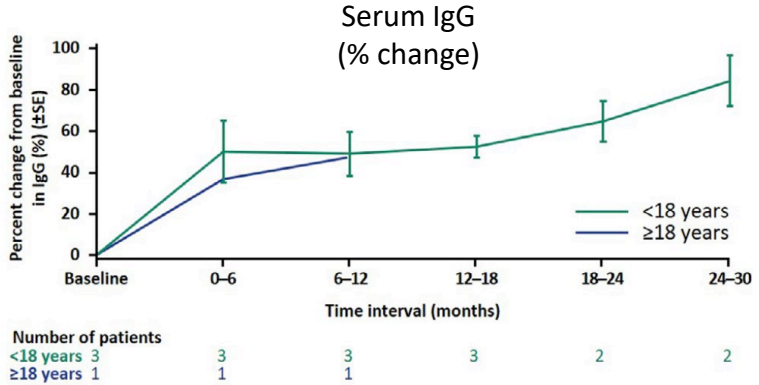
1. Borgwardt L, et al. *J Inherit Metab Dis*. 2018;41(6):1215-1223.
2. Lamzede. Prescribing information. Chiesi USA, Inc., 2023. Accessed January 7, 2026. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761278s000lbl.pdf

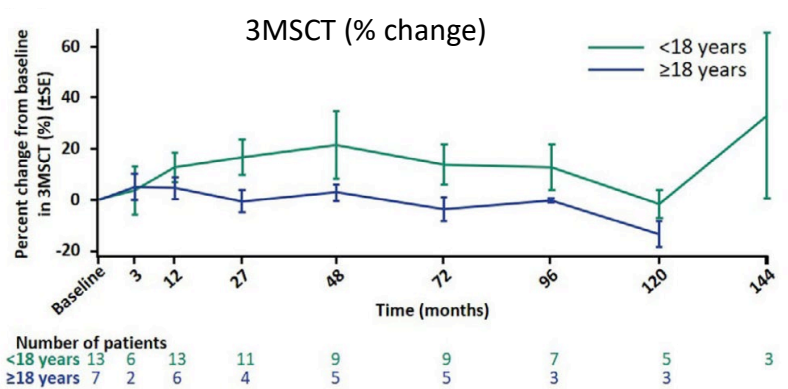
Long-Term Data

rhLAMAN-07 and rhLAMAN-09 (Phase 3b Trials) Pooled Analysis









IgG, immunoglobulin G; 6MWT, 6-minute walk test.

2024 Global Delphi Consensus Recommendations[1]

ERT-Related Monitoring	Preinfusion	Postinfusion	Every 6–12 mos	Yearly	As Clinically Indicated
Serum/urine oligosaccharide levels	X	X	X		
Antibody titers[a]			X		X
Infusion-related reactions[b]	X	X			
Comprehensive symptom-based monitoring				X	

[a]Antibody titers should be tested every 6–12 mos in all patients receiving ERT and as clinically indicated in patients who develop infusion-related reactions and/or have insufficient clinical response (high oligosaccharide levels).
[b]Administration of premedication and slowing the rate of ERT infusion should be considered if a patient has a high risk of developing infusion-related reactions.

1. Guffon N, et al. *Mol Genet Metab.* 2024;142(4):108519.

Considerations for HSCT in AM

- HSCT has been used for treating AM for decades[1,2]
  - Can improve neurologic and systemic symptoms and reduce disease burden
  - Associated with morbidity and mortality risks due to transplant complications
  - May not be an appropriate treatment option for all patients

- Patients and their caregivers have difficulty accessing transplant centers with experience in glycoproteinoses

1. Ceccarini M, et al. *Int J Mol Sci*. 2018;19(5):1500.
2. Stepien K, et al. *Orphanet J Rare Dis*. 2025;20(1):217.

Studies or Reports Involving HSCT in AM

Study	Details
Šáhó et al, 2025 Retrospective, multi-center study[1]	**21 children (11 female) with AM; median age at HSCT was 3.9 y** • Primary engraftment reached in 17 patients, 4 required a second HSCT • Outcomes suggest trends of higher functioning with earlier treatment
Mynarek et al, 2012[2] Retrospective, multi-institutional analysis	**17 patients diagnosed at a median of 2.5 y; HSCT at a median of 5.5 y of age** • Primary engraftment reached in 12 patients; 2 died within 5 mos, 3 required a second HSCT • Developmental improvement in all affected individuals • Preservation of previously learned skills in all affected individuals • Ability to participate in activities of daily living • Stabilization or improvement in skeletal abnormalities • Improvement in hearing ability in some affected individuals

Avenarius et al, 2011[3]	**1 patient (16 y) who received HSCT at age 10 y and 2 untreated patients (20 and 36 y) received proton nuclear magnetic resonance spectroscopy**
	• Compared to the untreated patients, the patient who received HSCT had:
	  • Diminished white matter abnormalities, reduced demyelination, and decreased gliosis
	  • Normalization of abnormal signals on spectroscopy

1. Šáhó R, et al. *J Inherit Metab Dis.* 2025;48(4):e70047.
2. Mynarek M, et al. *Bone Marrow Transplant*. 2012;47(3):352-359.
3. Avenarius DFM, et al. *J Inherit Metab Dis*. 2011;34(5):1023-1027.

2024 Global Delphi Consensus Recommendations[1]

Post-HSCT Monitoring
Serum/urine oligosaccharide and enzyme activity levels should be monitored for treatment effectiveness pre- and post-HSCT in all patients undergoing HSCT
Symptom-based evaluation should be conducted every 12 mos in all patients who have undergone HSCT
Monitoring of engraftment and HSCT-related complications (such as graft-versus-host disease and endocrine disorders) should be based on the recommendations of the hematologist/transplant team

Potential for Combining ERT and HSCT

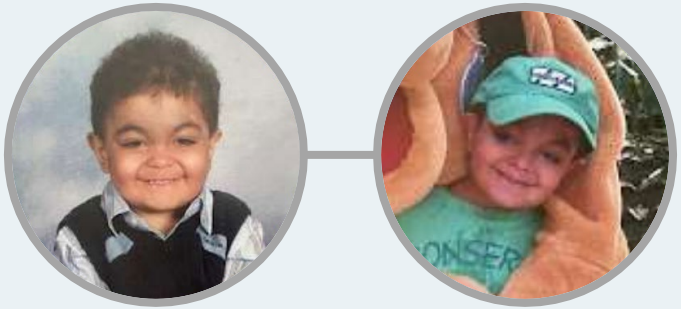
- Limited data for combining ERT and HSCT
- May be referred to as “bridge therapy”
- One published case study of a patient diagnosed at 5 mos who received ERT in the pre- and peri-transplant phases
  - 3 y post-HSCT show that the early combined intervention may reduce disease progression and urine/plasma oligosaccharides[1]

1. Santoro L, et al. *Am J Med Genet A*. 2023;191(7):1948-1952.

Case Vignette – Continued

Infancy	Early Childhood	**Childhood**	Early Adulthood

- HSCT performed at 17 mos of age with HLA-identical mother as donor
- Patient became fully engrafted
- No acute graft-versus-host disease but developed chronic graft-versus-host disease with skin, eye, and mucosal involvement
  - Other medical issues included:
    - Chronic otitis media with ear tubes placed at 4 y of age
    - Multiple dental caries requiring restorations under general anesthesia
    - Development delay with behavioral issues



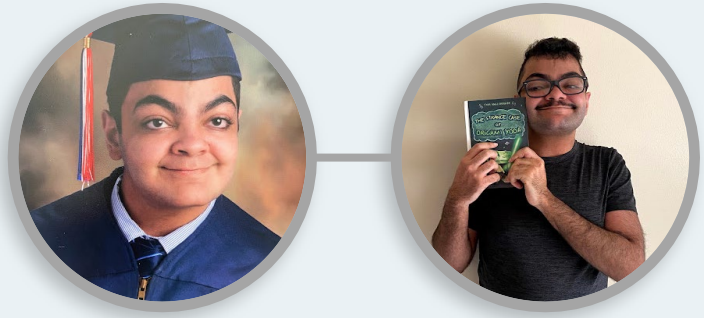
HLA, human leukocyte antigen.

Case study provided by Dr. Barbara Burton and shared with permission.

Case Vignette – Continued

Infancy	Early Childhood	Childhood	**Early Adulthood**

- Clinical observations:
  - Behavior issues resolved
  - Mild to moderate intellectual disability
  - Mild unilateral hearing loss
  - Normal immunoglobulins
- Started ERT at 19 y of age
- The patient reported:
  - Improved joint pain
  - Improved mobility



LCM, left costal margin; RCM, right costal margin.

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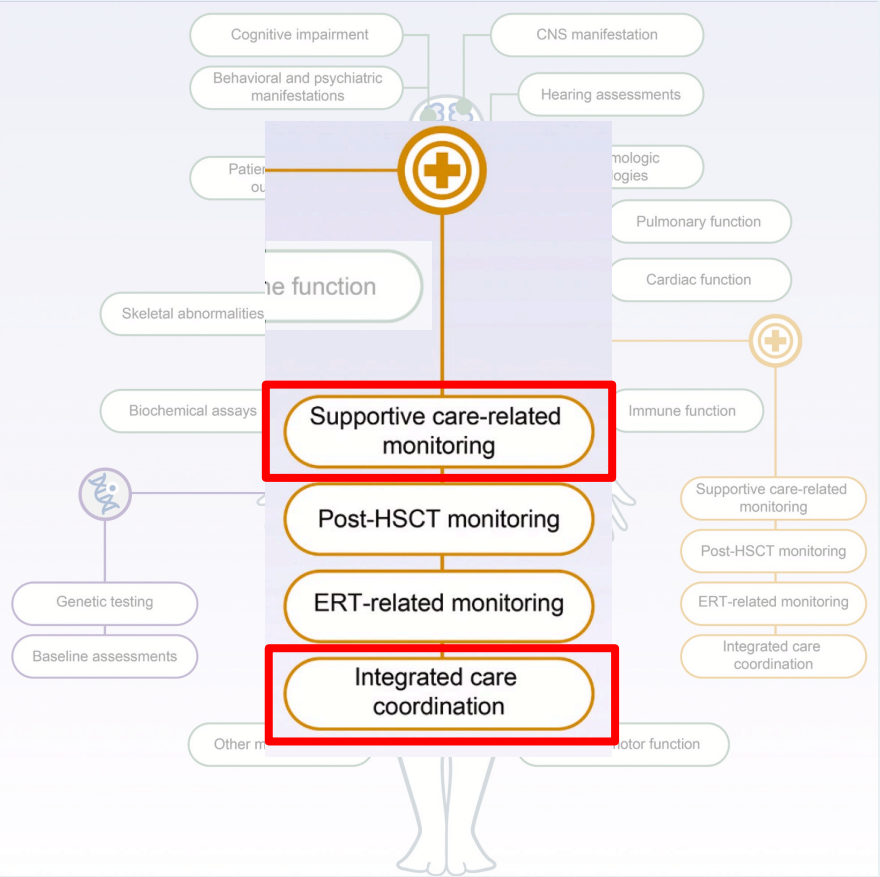
2024 Global Delphi Consensus Recommendations[1]

Key area 1:
Assessments in newly diagnosed patients

Key area 2:
Routine follow-up care

Key area 3:
Treatment-related follow-up care



2024 Global Delphi Consensus Recommendations[1]

Integrated Care Coordination

Patients with AM should have a long-term multidisciplinary care team that includes an AM specialist (geneticist/metabolic specialist and a group of specialists including (but not limited to):

- Audiologist
- Otolaryngologist
- Cardiologist
- Ophthalmologist
- Orthopedic specialist
- Pediatrician
- Physiotherapist
- Occupational therapist
- Pulmonologist
- Social and family therapist
- Psychologist
- Imaging specialist
- Speech and language therapist

Where possible, patients with AM should be seen in a multidisciplinary clinic.

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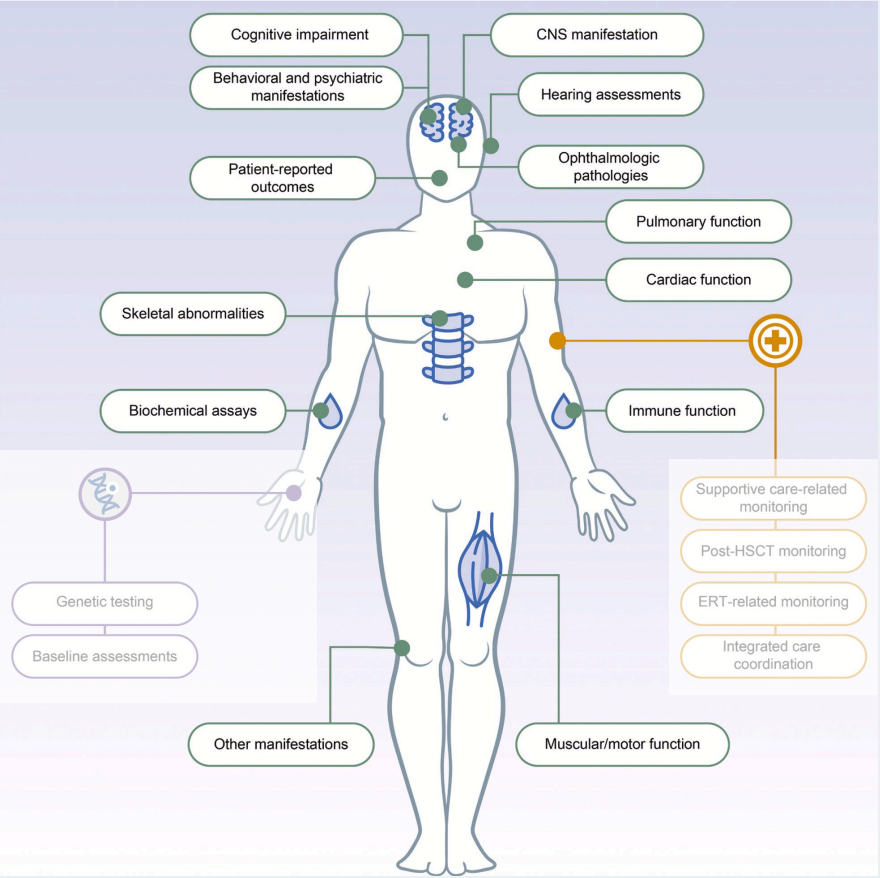

2024 Global Delphi Consensus Recommendations[1]

Routine Follow-Up Care
Muscular or motor function: monitor for muscular and motor function problems at every visit (at least every year), including neurologic examination, balance and coordination tests, and patient-reported symptom assessment; conduct specific motor function assessments every 6–12 mos in pediatric patients (every year in adults) depending on ability; assessment and follow-up with physical or occupational therapist as needed
Skeletal abnormalities: monitor for skeletal abnormalities by clinical examination at least every year; refer to orthopedic specialists if surgical or other specific interventions needed; skeletal imaging, bone density tests (adults), and physiotherapy tests performed as needed or based on disease severity and age
Cognitive Function: monitor for cognitive delay or decline; conduct cognitive function assessments yearly in pediatric patients; formal assessments at periods of key transitions, change in environment, or disease progression; referral to specialist as needed or based on clinical assessments

Adapted from Guffon N, et al. *Mol Genet Metab*. 2024;142(4):108519 under Creative Commons CC-BY 4.0 license. https://creativecommons.org/licenses/by/4.0/legalcode

2024 Global Delphi Consensus Recommendations[1]

Routine Follow-Up Care (continued)
Behavioral and psychiatric manifestations: monitor for behavioral problems; patient history and symptom-based screening every 1–2 years; referral to psychiatrist/psychologist as needed
Central nervous system manifestations: monitor for potential neurological symptoms; physical and neurologic examination every 6 mos (<4 y of age) or yearly (≥4 y of age); brain imaging when needed
Hearing loss: standard audiometry assessment should be performed every 1–2 years; pediatric patients with hearing aids should be monitored at least every 6–12 mos; otoscopic evaluation at least every year
Biochemical assays: conduct annual biochemical lab assessments such as those that screen for liver and kidney issues, blood glucose levels, fluid and electrolyte balance, and blood count

2024 Global Delphi Consensus Recommendations[1]

Routine Follow-Up Care (continued)
Pulmonary function: assess respiratory function regularly; conduct yearly pulmonary function tests in patients able to complete testing; monitor for signs of respiratory difficulties and conduct additional workup if needed
Cardiac function: monitor for hypertension, cardiomyopathy, and exercise intolerance; cardiac function assessment should be conducted every 2–3 years; refer to cardiology if cardiac abnormalities expected
Ophthalmologic pathologies: monitor visual acuity and night acuity for myopia, hyperopia, and other ophthalmic disorders; ophthalmic examination at least every year, or every 6 mos if worsening pathology
Immune function: monitor immunoglobulin levels and assess for signs of immune dysfunction and infections; conduct relevant laboratory assessments, and encourage routine vaccinations for all patients with AM

2024 Global Delphi Consensus Recommendations[1]

Routine Follow-Up Care (continued)
Patient-reported outcomes: regularly monitor school/work performance, disease burden, quality of life, motor skills, cognitive skills, and social competence, as well as caregiver quality of life and well-being
Other manifestations: monitor for dental quality and incidence of dental caries, endocrine disorders, growth problems, and unusual behaviors/new symptoms as clinically indicated