Improving the alpha-mannosidosis patient journey

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Improving first steps in the patient journey: How important is early recognition of alpha-mannosidosis?

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Why is early recognition of alpha-mannosidosis so clinically challenging?

Challenges in clinical recognition of AM

Alpha-mannosidosis is a rare 'ultra-orphan' lysosomal storage disorder[1,2]

Estimated prevalence[3]

0.1 in 100,000

Rarity and varying severity of disease presents clinical challenges[4]

Understanding disease natural history[1]

Delayed recognition[4]

Underdiagnosis[5]

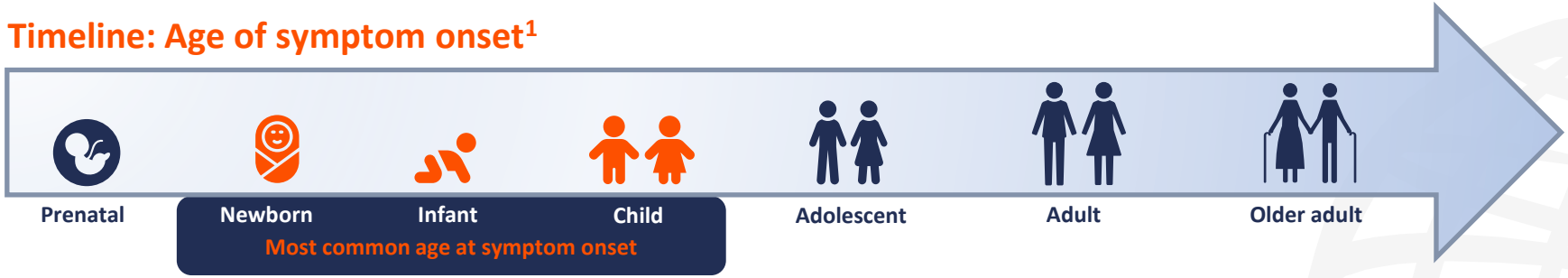
AM, alpha-mannosidosis.

1. Garbade SF, et al. *J Inherit Metab Dis.* 2021;44:99–109; 2. Zielonka M, et al. *J Inherit Metab Dis.* 2019;42:975–83;
3. Orphanet Report Series. Available at: www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_decreasing_prevalence_or_cases.pdf (accessed 16 December 2022); 4. Hennermann JB, et al. *Orphanet J Rare Dis.* 2022;17:287. 5. Wiesinger T, et al. *Mol Genet Metab*. 2020;130:149–52.

What do we currently know about the natural history of alpha-mannosidosis?

Overview of AM

Timeline: Age of symptom onset[1]



Clinical subtypes[2]

Type 3

Severe form

- Immediately recognized due to skeletal abnormalities
- Obvious progression
- Early death from primary CNS involvement or myopathy

Type 2

Moderate form (most common)

- Clinically recognized before 10 years of age
- Skeletal abnormalities
- Slow progression
- Development of ataxia at age 20–30

Type 1

Clinically mild form

- Recognized after 10 years of age
- No prominent skeletal abnormalities
- Slow progression

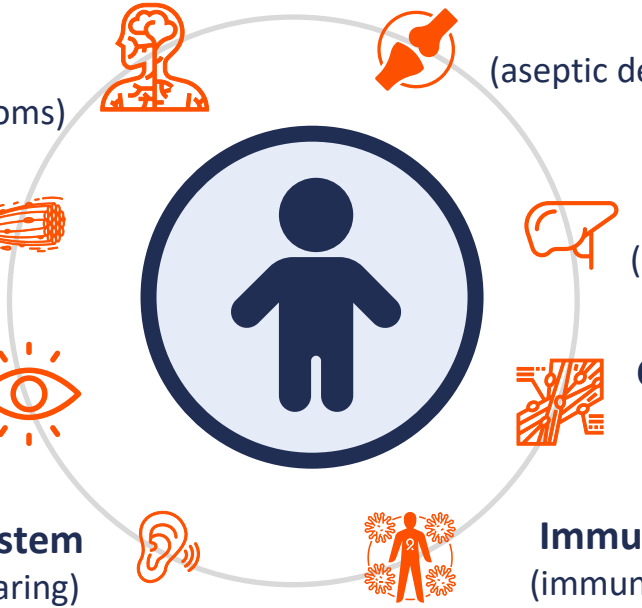
AM, alpha-mannosidosis; CNS, central nervous system.

1. Genetic and Rare Diseases Information Center. Available at: https://rarediseases.info.nih.gov/diseases/6968/alpha-mannosidosis (accessed 16 December 2022);
2. Malm D, Nilssen Ø. *Orphanet J Rare Dis.* 2008;3:21.

What are the key signs and symptoms associated with alpha-mannosidosis that we should look out for in the clinic?

Prominent signs and symptoms in patients with AM

Organ systems affected



Central nervous system
(ataxia, intellectual disability, hydrocephalus, psychiatric symptoms)

Joints
(aseptic destructive arthritis)

Muscles
(metabolic myopathy)

Visceral organs
(hepatosplenomegaly)

Eyes
(corneal opacities)

Connective tissue
(coarse features)

Auditory system
(impaired hearing)

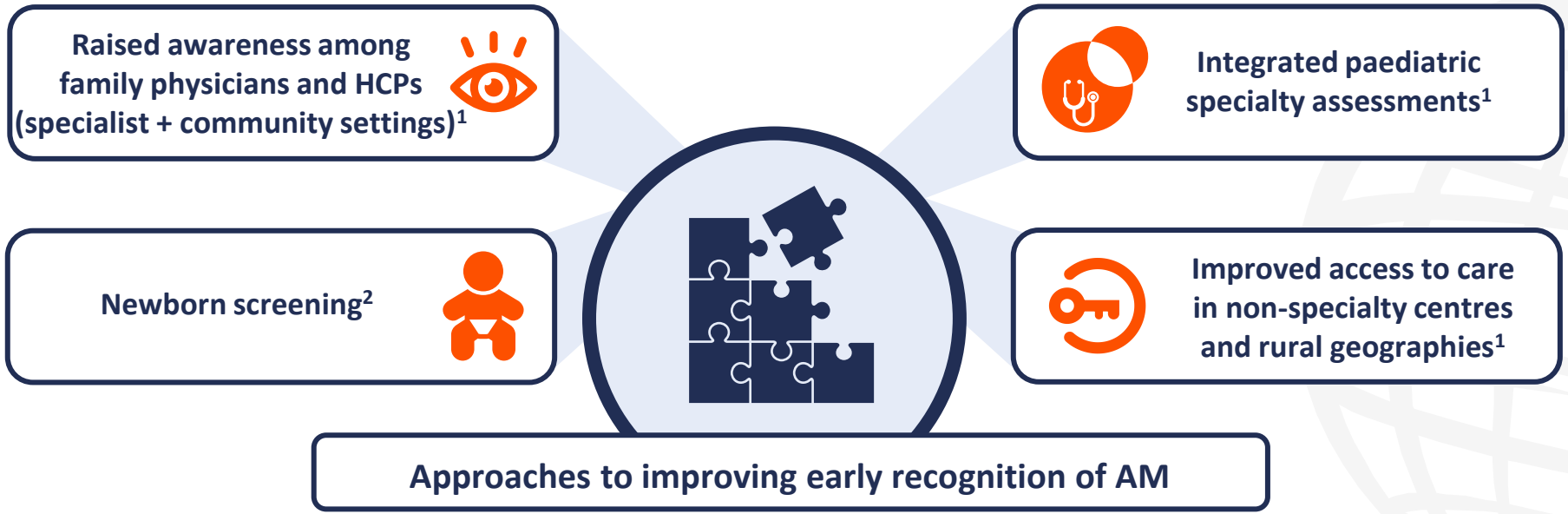
Immune system
(immunodeficiency)

AM, alpha-mannosidosis.

1. Zielonka M, et al. *J Inherit Metab Dis*. 2019;42:975–83.

How could we improve early recognition of alpha-mannosidosis, now and in the future?

Addressing barriers to early recognition of AM



SPARKLE registry
Patient registry and real-world data are needed to:[3]

- *Better understand disease natural history*
- *Identify early signs/symptoms*
- *Characterize biomarkers/predictors of clinical course*

AM, alpha-mannodosis; HCP, health care professional. 1. Verrecchia E, et al. *Adv Ther.* 2021;38:1–10; 2. Malm D, Nilssen Ø. Alpha-mannosidosis. 2001 (updated 2019). Available at: www.ncbi.nlm.nih.gov/books/NBK1396/ (accessed 16 December 2022); 3. Hennermann JB, et al. *Orphanet J Rare Dis.* 2020;15:271.

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Supporting early diagnosis: What more is needed?

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What warrants an index of clinical suspicion for alpha-mannosidosis? Does this change with age of presentation?

Prominent signs and symptoms suggestive of AM

Patients ≤10 years[1]

- Speech delay
- Hearing loss
- Developmental delay
- Motor disturbances/joint laxity
- Infections
- Facial features
- Mild hepatosplenomegaly
- Hernia

Patients >10 years[1]

- Hearing loss
- Ataxia
- Psychiatric disorder
- Not prominent skeletal disorder
- Intellectual disability

AM, alpha-mannosidosis.

1. Guffon N, et al. *Mol Genet Metab*. 2019;126:470–4.

How do we reach a diagnosis of alpha-mannosidosis?

Route to diagnosis in AM

Clinical → **Biochemistry** → **Enzymology** → **Genetics**

Physical signs + symptoms[1,2]

- Facial features
- Musculoskeletal
- Auditory
- Immunodeficiency
- Developmental

Urine analysis[1,2]

- High levels of mannose-rich oligosaccharides

Enzyme activity[1,2]

- Acid alpha-mannosidase activity 5–10% normal activity in peripheral blood leukocytes

Confirmatory genetics[1,2]

- *MAN2B1* variants

AM, alpha-mannosidosis; MAN2B1, mannosidase alpha class 2B member 1.

1. Malm D, Nilssen Ø. Alpha-mannosidosis. 2001 (updated 2019). Available at www.ncbi.nlm.nih.gov/books/NBK1396/ (accessed 16 December 2022);
2. Guffon N, et al. *Mol Genet Metabol.* 2019;126:470–4.

How informative are genetic tests for pathogenic variants to guide clinical management decisions in alpha-mannosidosis?

Role of *MAN2B1* pathogenic variants in AM

Deficient alpha-mannosidase enzyme activity owing to mutations in the *MAN2B1* gene (location: chromosome 19p13.13)[1,2]

162 ***MAN2B1* variants reported[1]**

- **No clearly established genotype–phenotype correlation[1,2]**
- **Phenotypic variability between genotypically identical siblings[3]**
- **If *MAN2B1* variants of uncertain significance are identified on WES, further tests are required to establish a diagnosis of AM[4,5]**

AM, alpha-mannosidosis; MAN2B1, mannosidase alpha class 2B member 1; WES, whole-exome sequencing.

1. Hennermann JB, et al. *Orphanet J Rare Dis.* 2022;17:287; 2. Lipinski P, et al. *Mol Genet Metab Rep.* 2022;30:100826; 3. Borgwardt L, et al. *Orphanet J Rare Dis.* 2015;10:70; 4. Malm D, Nilssen Ø. Alpha-mannosidosis. 2001 (updated 2019). Available at: www.ncbi.nlm.nih.gov/books/ (accessed 16 December 2022); 5. Correspondence with faculty (Prof. Barbara K Burton; 17 January 2023).

How can we address the challenges associated with timely and accurate differential diagnosis?

Differential diagnosis of AM from other LSDs

Clinical and laboratory features of the disorders[1]

Overlapping with AM	Disorders	Distinguishing from AM
Coarse facial features, dysostosis multiplex, intellectual disability	**Mucopolysaccharidoses**	Short stature, contractures
Coarse facial features, dysostosis multiplex	**Mucolipidosis II**	Short stature, failure to thrive
Coarse facial features, dysostosis multiplex	**Mucolipidosis III alpha/beta**	Short stature, normal-to-mildly impaired cognitive development
Coarse facial features, dysostosis multiplex, intellectual disability	**Sialidosis**	Cherry red spot of the macula
Hypotonia, coarse facial features, developmental delay, frequent upper-respiratory infections	**Sialuria**	Joint stiffness, seizures, microcytic anaemia
Coarse facial features, thickened ribs	**Cantú syndrome**	Heart defects, hypertrichosis

AM, alpha-mannosidosis; LSD, lysosomal storage disorder.

1. Malm D, Nilssen Ø. Alpha-mannosidosis. 2001 (updated 2019). Available at: www.ncbi.nlm.nih.gov/books/NBK1396/ (accessed on 19 December 2022).

Why is a timely and accurate diagnosis so important in alpha-mannosidosis?

Optimizing outcomes in AM

Early diagnosis is crucial to support outcomes with treatment beyond symptom management and supportive care[1,2]

If untreated, prognosis remains poor, but many patients live to ≥50 years of age[2]

Progressive disease course with cognitive, neuromuscular and skeletal deterioration over several decades[2]

Most patients eventually become wheel-chair dependent[2]

Pneumonia has been the primary cause of death during recent decades in untreated patients, followed by cancer[1]

Hearing loss as one of the first noted symptoms is congenital and non-progressive during disease course[3]

Untreated patients have worsening white matter abnormalities, diminished myelination, and gliosis[4]

Delays in diagnosis and treatment can lead to cumulative morbidity that may require long-term residential care needs[5]

AM, alpha-mannosidosis.

1. Hennermann JB, et al. *Orphanet J Rare Dis.* 2022;17:287; 2. Guffon N, et al. *Mol Genet Metabol.* 2019;126:470–4;
3. Lipinski P, et al. *Mol Genet Metab Rep.* 2022;30:100826; 4. Naumchik BM, et al. *Cells.* 2020;9:1411; 5. Verrecchia E, et al. *Adv Ther.* 2021;38:1–10.

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Optimizing outcomes in alpha-mannosidosis: How might current and emerging targeted therapies address long-term needs?

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What is the current standard of care for alpha-mannosidosis?

Symptomatic and supportive measures in AM

Treatment aims to prevent and/or manage complications associated with AM

- Hearing aids, pressure-equalising tubes
- Regular eye and dental check-ups
- Antibiotic prophylaxis to prevent infection(s)
- Speech and language therapy, educational support
- Orthopaedic interventions for skeletal abnormalities, spinal deformities, polyarthropathy
- Counselling, psychosocial support

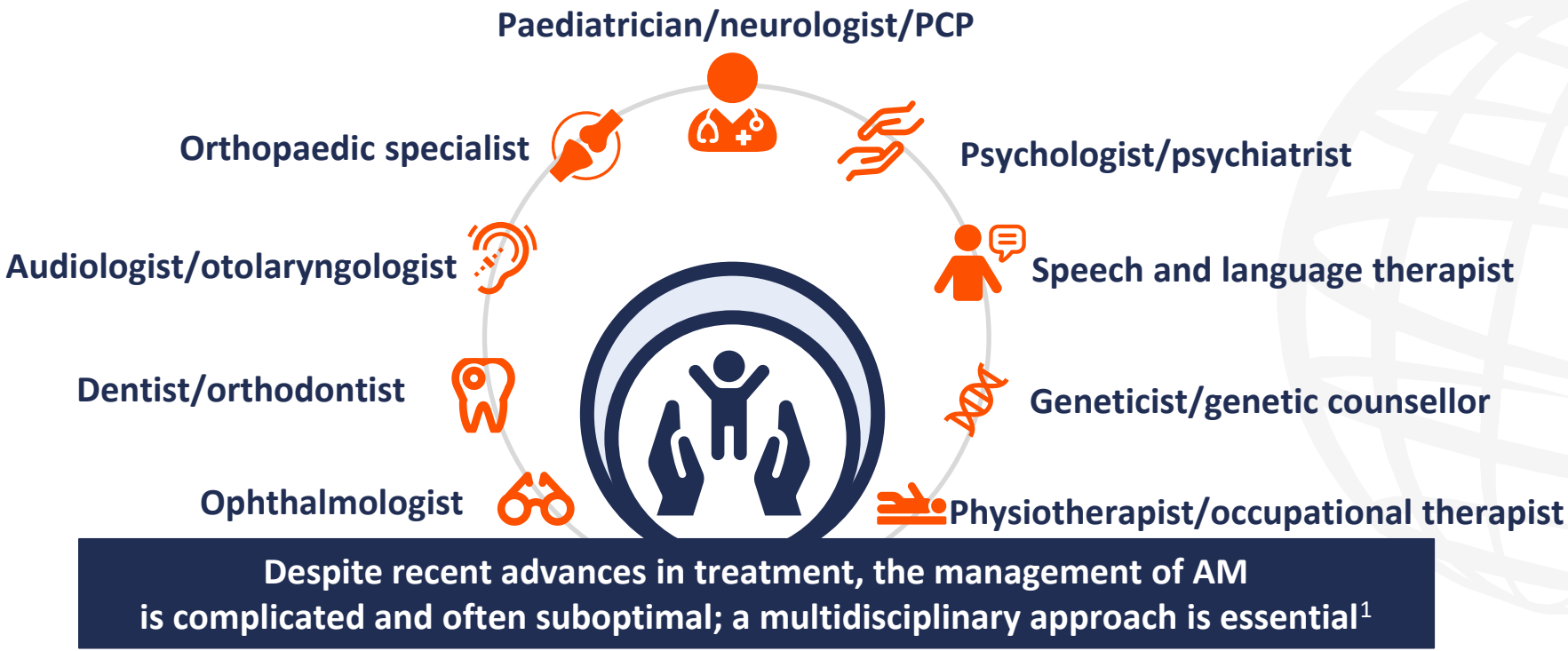
Pro-active early intervention is imperative to ensure children with AM reach their maximum potential

AM, alpha-mannosidosis.

NORD. Alpha-mannosidosis. 2018. Available at: https://rarediseases.org/rare-diseases/alpha-mannosidosis/ (accessed 19 December 2022).

Why is multidisciplinary management so important?

MDT management of AM as a multisystem disorder[1–4]



Despite recent advances in treatment, the management of AM is complicated and often suboptimal; a multidisciplinary approach is essential[1]

AM, alpha-mannosidosis; MDT, multidisciplinary team; PCP, primary care provider.

1. Guffon N, et al. *Mol Genet Metabol.* 2019;126:470–4; 2. Genetic and Rare Diseases Information Center. Available at: https://rarediseases.info.nih.gov/diseases/6968/alpha-mannosidosis (accessed 20 December 2022); 3. Adam J, et al. *Mol Genet Metabol.* 2019;20:100480.

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How might therapies address long-term needs in alpha-mannosidosis?

Harnessing therapies to address long-term needs in AM

Approaches to minimize storage material accumulation and irreversible pathology

HSCT[1]	Introduce functional enzyme-producing cells into blood and bone marrow, with healthy donor cell CNS engraftment
ERT[2,3]	Promote storage clearance with exogenous functional enzyme
PCT[2,3]	Enhance activity of misfolded enzyme
SRT[2]	Inhibit substrate synthesis to prevent accumulation in lysosomes

Role of therapies to support outcomes in AM

- Prevent early mortality[3]
- Preserve neurocognitive function[3,4]
- Stabilize and support skeletal development[3]
- Prevent cumulative multisystem morbidity[3–5]
- Support life goals and maximize QoL[3–5]

AM, alpha-mannosidosis; CNS, central nervous system; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplant; PCT, pharmalogical chaperone therapy; QoL, quality of life; SRT, substrate reduction therapy.

1. Naumchik BM, et al. *Cells.* 2020;9:1411; 2. Diaz JCL, et al. *Int J Mol Sci.* 2022;1:232; 3. Ceccarini V, et al. *Int J Mol Sci.* 2018;19:1500; 4. Verrecchia E, et al. *Adv Ther.* 2021;38:1-10; 5. Cathey S, et al. *JIMD Rep.* 2019;50:44–9.

What therapy approaches are currently available?

Current treatment landscape in AM

HSCT[1]

Introduce functional enzyme-producing cells into blood and bone marrow, with healthy donor cell CNS engraftment

Data are limited but studies show HSCT attenuates CNS disease, alleviating neuropathology[1]

Minimizes pathological lysosomal accumulation of mannose-rich oligosaccharides and associated morbidity, notably:

neurologic function and skeletal development[1]

88% **survival rate with stable engraftment** (5.5 years median follow-up) n = 17[2]

Patients achieved cognitive developmental progress post-HSCT[2]

ERT[3]

Promote storage clearance with exogenous functional enzyme

rhLAMAN (velmanase alfa) studies: Long-term data[4]

Velmanase alfa improved biochemical and functional measures that were maintained up to 4 years

sOLIGO clearance (Δ baseline to 12 months)
−72.7%; 95% CI −81.4, −64.1; p<0.001

n = 31

3MSCT (Δ baseline to 12 months)
+9.3%; 95% CI 2.14, 16.5; p=0.013

Early treatment during paediatric age associated with better functional outcomes

Δ, mean change; 3MSCT, 3-minute stair climb test; AM, alpha-mannosidosis; CI, confidence interval; CNS, central nervous system; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplant; rhLAMAN, recombinant human lysosomal alphamannosidase; sOLIGO, serum oligosaccharides.

1. Naumchik BM, et al. *Cells*. 2020;9:1411; 2. Mynarek M, et al. *Bone Marrow Transpl.* 2012;47:352–9; 3. Ceccarini V, et al. *Int J Mol Sci*. 2018;19:1500; 4. Lund AM, et al. *J Inherit Metab Dis.* 2018;41:1225–33.

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What role might enzyme replacement and pharmacological chaperone therapies play in the future management of alpha-mannosidosis?

Improving outcomes: Continuing our focus on earlier intervention

Newborn screening	May facilitate earliest intervention and prevention of clinical manifestations[1,2]
Recognition[1–3]	Earliest possible recognition of the possibility of AM in patients is key[1–3]
Diagnosis[1–3]	Timely and accurate differential diagnosis to initiate appropriate management[1–3]
Treatment[2,3,5,6]	Earlier treatment associated with positive outcomes; wider access to therapies where possible[2,3,5,6]
Research[4]	Other therapies may continue to further improve the patient journey[4]

Support best outcomes for people living with AM, to achieve life goals and maximize QoL[2]

AM, alpha-mannosidosis; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplant; QoL, quality of life. 1. Malm D, Nilssen Ø. Alpha-mannosidosis. 2001 (updated 2019). Available at: www.ncbi.nlm.nih.gov/books/NBK1396/; 2. Guffon N, et al. *Mol Genet Metabol.* 2019;126:470–4; 3. Adam J, et al. *Mol Genet Metabol.* 2019;20:100480; 4. Garbade SF, et al. *J Inherit Metab Dis.* 2021;44:99–109; 5. Ceccarini V, et al. *Int J Mol Sci*. 2018;19:1500; 6. Lund AM, et al. *J Inherit Metab Dis.* 2018;41:1225–33).