DISCOVER
Alpha Mannosidosis

Alpha-mannosidosis

Recognising “red flags” to aid early diagnosis

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Chiesi
global rare diseases

Awareness is key to diagnosis[1]

Patients with rare diseases face a 'diagnostic odyssey', undergoing a myriad appointments and procedures with the aim of a definitive diagnosis.[2] Despite this, patients often remain undiagnosed or even misdiagnosed.[2]

This can result in:[1]

- Anxiety and mental ill health
- Difficulty in expressing care requirements and unmet needs
- Inappropriate treatment or a delay of effective treatment

Key facts

An accurate diagnosis of a rare disease takes an average of 4–5 years; in some cases, it can take over a decade[2]

Most patients suffering from a rare or undiagnosed disease receive only symptomatic treatment[2]

An estimated 80% of rare diseases have a genetic origin[2]

For patients with a rare disease, a delay in diagnosis is contributed to by:[3]

- A lack of scientific knowledge surrounding rare diseases
- The presence of widely varying non-specific symptoms that overlap with other conditions

An accurate diagnosis can result in better management of the disease, including identification of therapeutics[2]

Lysosomal storage disorders

Lysosomal storage disorders are a group of rare or ultra-rare conditions caused by a deficiency in certain enzymes.[4]

Alpha-mannosidosis

Alpha-mannosidosis is **a type of lysosomal storage disorder** caused by the deficiency of alpha-mannosidase.[5]

As an **ultra-rare condition**, alpha-mannosidosis has a high potential for differential diagnosis.[6]

The main clinical features in alpha-mannosidosis may overlap with other lysosomal storage diseases, e.g., **mucopolysaccharidosis (MPS).**[4]

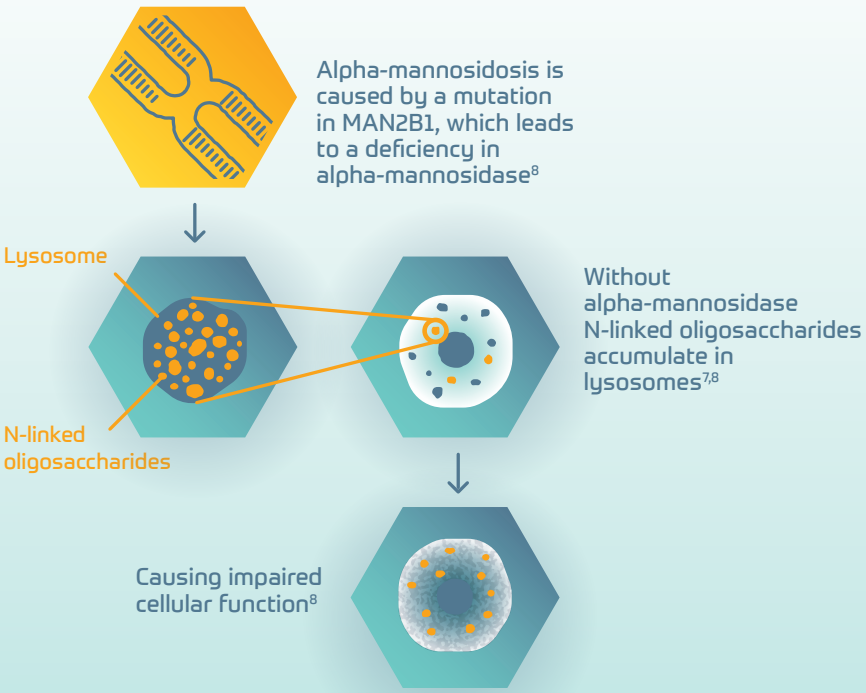
How common is alpha-mannosidosis?

Alpha-mannosidosis is extremely rare; it is thought to occur in around **1 in 500,000 to 1 in 1,000,000 births** worldwide.[5]

1 in 500,000 to
1 in 1,000,000

What is alpha-mannosidosis?

Alpha-mannosidosis is caused by the deficiency of alpha-mannosidase, leading to accumulation of mannose-rich oligosaccharides in all tissues and resulting in impaired cellular function and apoptosis.[7,8]

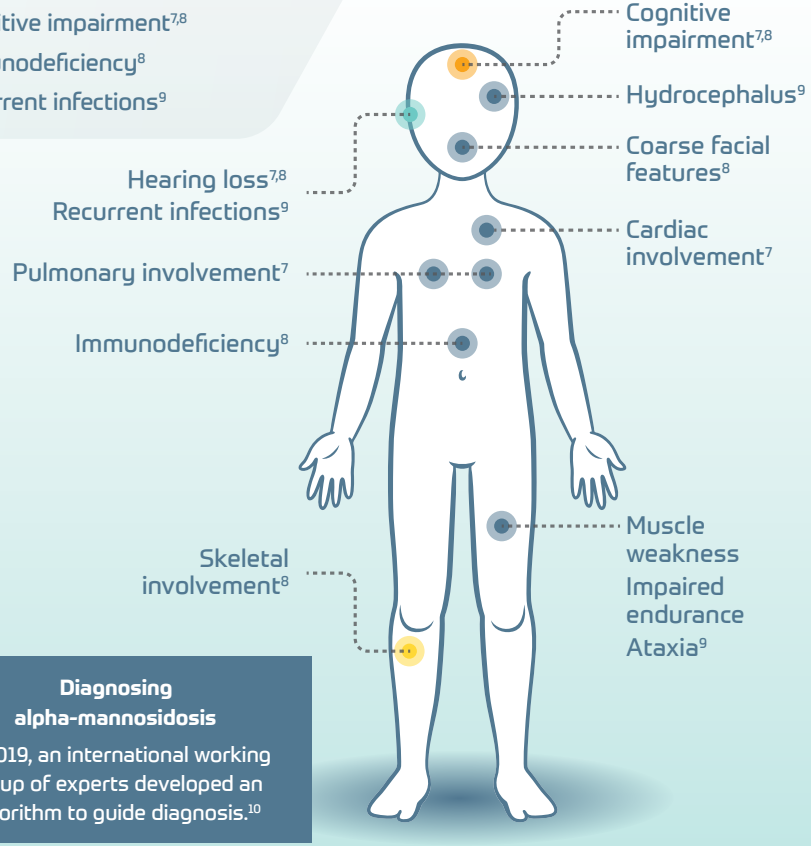


Clinical presentation of alpha-mannosidosis

Alpha-mannosidosis presents with broad heterogeneity of symptoms.[7-9]

Some of the main features are:

- Hearing loss[7,8]
- Skeletal involvement[8]
- Cognitive impairment[7,8]
- Immunodeficiency[8]
- Recurrent infections[9]



Diagnosing alpha-mannosidosis

In 2019, an international working group of experts developed an algorithm to guide diagnosis.[10]

Hearing loss in alpha-mannosidosis

Patients with alpha-mannosidosis suffer from a combination of conductive and sensorineural hearing loss.[7]

- In a natural history study evaluating clinical and surrogate parameters of 43 alpha-mannosidosis patients:[7]

100%

of patients over the age of 3 years had significant hearing loss and had to wear hearing aids.[7]

- In the clinical development programme of velmanase alfa, baseline analysis of 33 patients revealed that:[11]

97%

of patients had impaired* or seriously impaired† hearing.[11]

*26–55 dBHL; best ear bone conduction. †≥56 dBHL; best ear bone conduction.

How important is hearing loss when diagnosing alpha-mannosidosis?

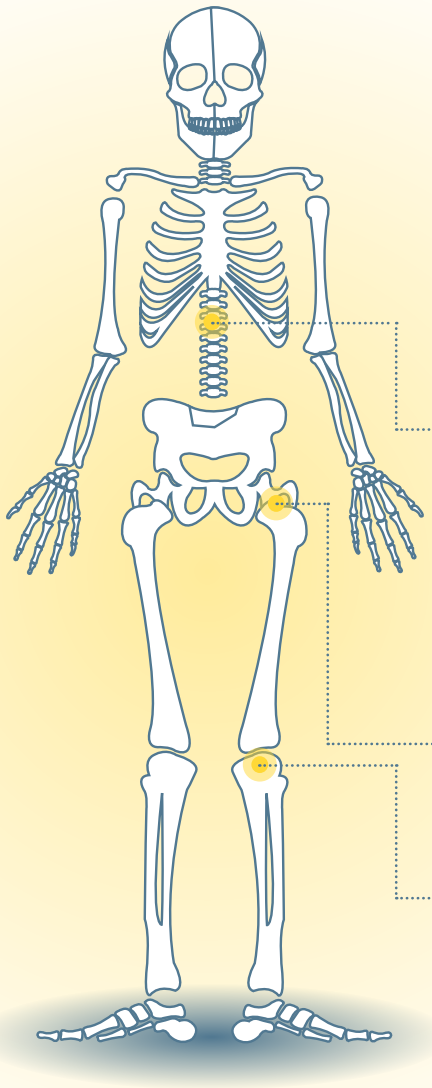
Hearing loss is an important and early manifestation of alpha-mannosidosis.[12]

In 2019, Lehalle and colleagues reported cases of 7 patients referred to clinical geneticists for syndromic hearing loss and moderate cognitive impairment that were diagnosed with alpha-mannosidosis.[12]

The authors suggest that hearing loss, especially when associated with learning or cognitive difficulties, with or without dysmorphic features, should raise a possible diagnosis of lysosomal storage disorder – in particular, alpha-mannosidosis.[12]

The broad phenotypic spectrum of alpha-mannosidosis combined with the molecular heterogeneity of genetic deafness highlight the value of exome sequencing for establishing early diagnoses of rare disorders.[12]

Skeletal involvement in alpha-mannosidosis



Bone anomalies are one of the most common manifestations of alpha-mannosidosis, as reported by Zielonka and colleagues in a quantitative analysis of published cases.[13]

62% of patients <18 years and **92%** of patients ≥18 years have skeletal abnormalities, such as **joint contractures, scoliosis, genua valga** and **hip dysplasia**[7]

Study design: Natural history study evaluating clinical and surrogate parameters of 43 alpha-mannosidosis patients

90% of patients show clinical or radiographic signs of **mild-to-moderate dysostosis multiplex**[9]

From the **second to the fourth decade of life**, patients may develop destructive polyarthropathy, including coxarthrosis and gonarthrosis[9]

Cognitive impairment in alpha-mannosidosis

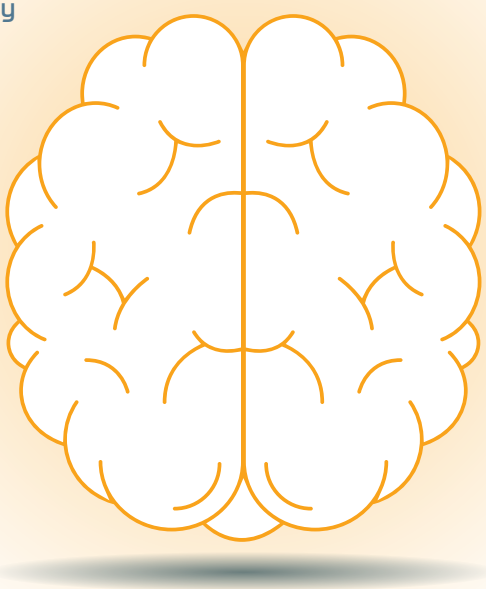
Cognitive impairment is one of the most common manifestations of alpha-mannosidosis.[7]

In a clinical study of 8 patients with alpha-mannosidosis:[9]

- Symptoms typically began with delayed development of speech or motor or mental functions.[9]
- All patients showed mild or moderate mental retardation, with an IQ of 60–80 and a declining tendency over later decades.[9]

Patients with alpha-mannosidosis are also at an increased risk of **psychiatric symptoms**, with 25% of patients affected.[8]

- First onset of symptoms usually occurs in late puberty to early adolescence.[5]
- Episodes generally last 3–12 weeks and may be recurrent.[5]
- Symptoms include confusion, hallucinations, anxiety and depression.[5]



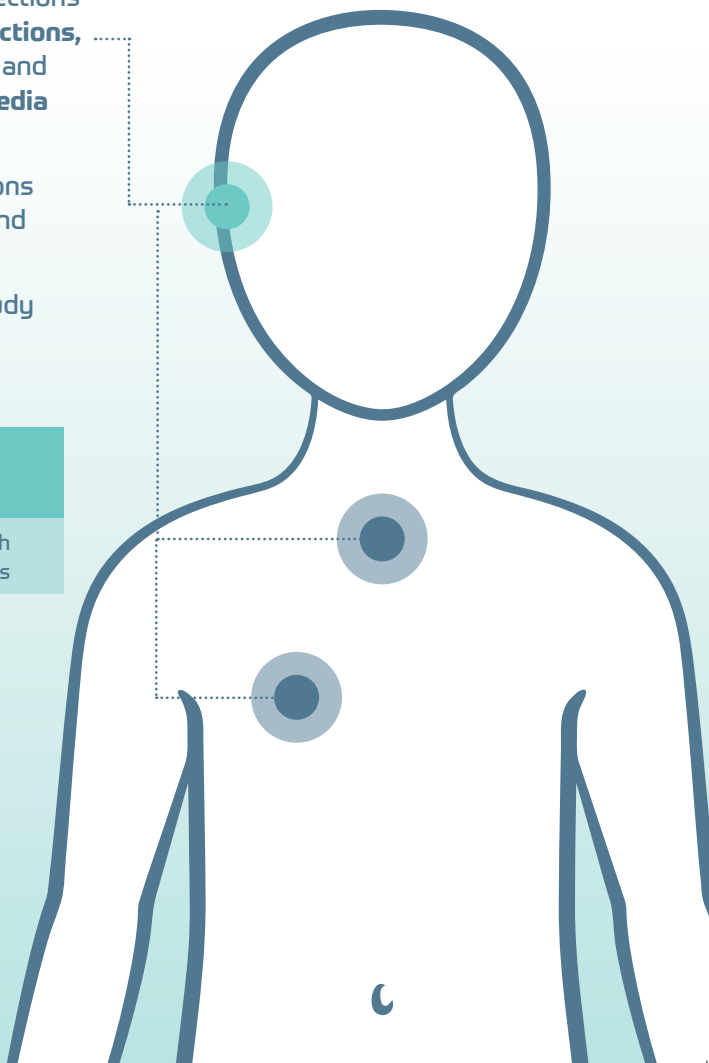
Recurrent infections

Patients with alpha-mannosidosis frequently have recurrent infections, especially in the first 10 years.[5]

- The most common infections are: **upper airway infections, pulmonary infections** and **acute/serous otitis media infections**[5]
- The number of infections diminishes in the second and third decades[5]
- In a natural history study of 111 patients with alpha-mannosidosis:[13]

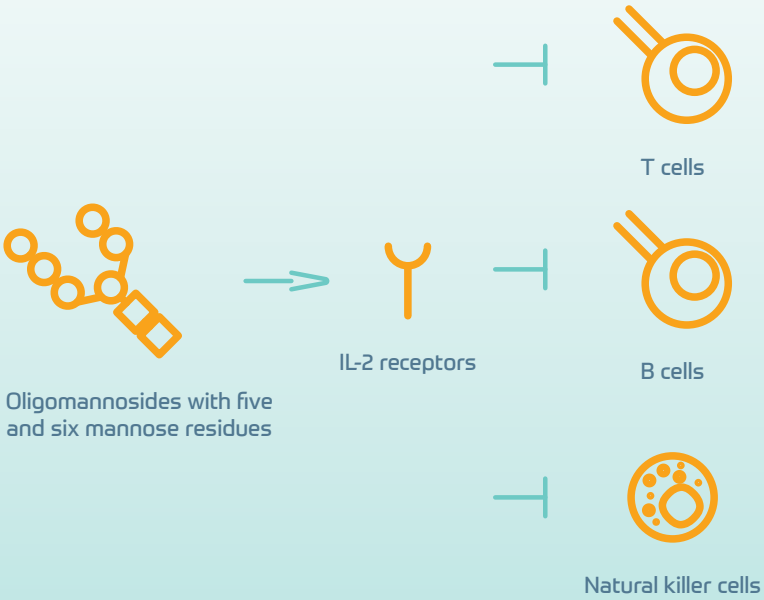
53%

of patients presented with respiratory tract infections



Immunodeficiency

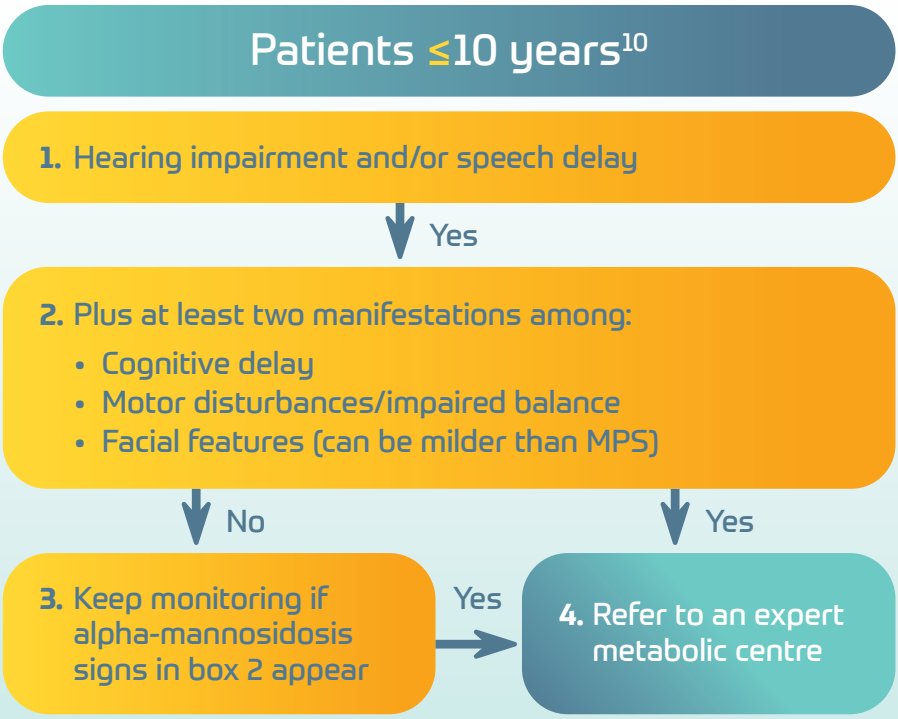
- Alpha-mannosidosis patients have increased levels of oligosaccharides in plasma. These are able to bind to interleukin-2 (IL-2) receptors, disturbing IL-2-dependent activation of T cells, B cells and natural killer cells. Blockage of this receptor may be the mechanism behind immunodeficiency in alpha-mannosidosis.[9]
- In a comparison of six alpha-mannosidosis patients to six age- and sex-matched healthy controls, post-immunisation antibody levels were lower in patients, showing decreased antibody production in response to antigen presentation.[9]
- Evidence of reduced phagocytosis and impaired leukocyte chemotaxis has also been found in alpha-mannosidosis patients.[9]



Diagnosing alpha-mannosidosis

≤10 years

In 2019, with no internationally recognised guidelines for early group of experts met to establish an algorithm to help general achieve early diagnosis and initiate adequate treatment as



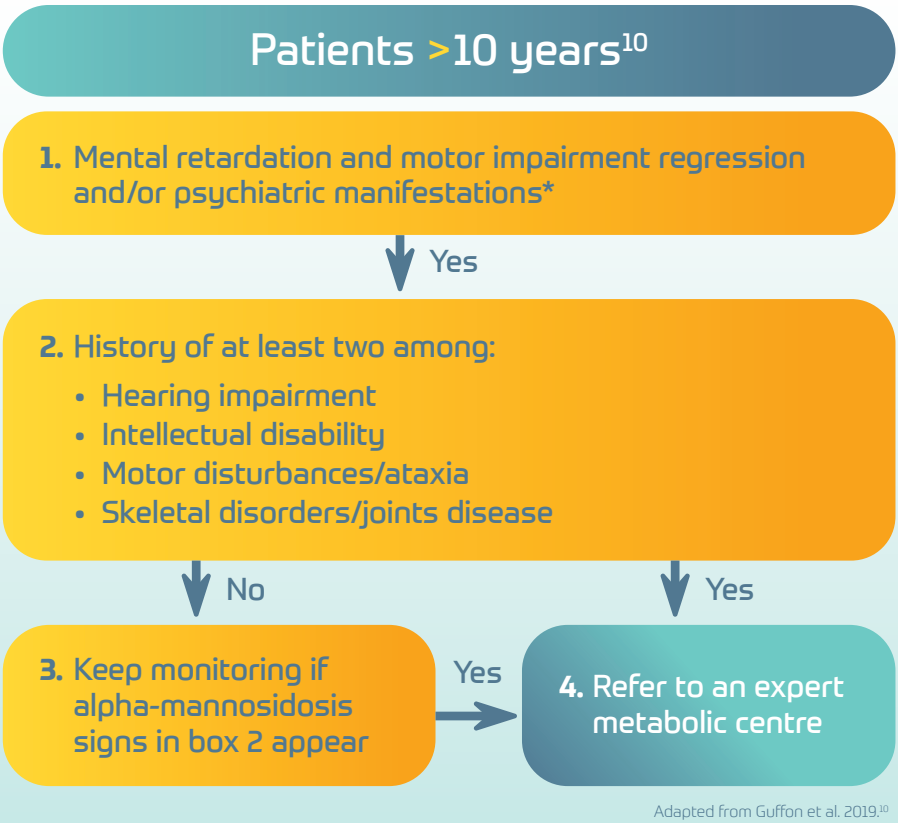
Adapted from Guffon et al. 2019.[10]

MPS = mucopolysaccharidosis.

Diagnosing alpha-mannosidosis

>10 years

diagnosis of alpha-mannosidosis, an international working
practitioners and specialists (metabolic and non-metabolic)
soon as possible.[10]



Adapted from Guffon et al. 2019.[10]

*Includes acute psychotic events.

Refer

If alpha-mannosidosis is suspected based on medical history or physical examination, additional monitoring or referral for testing is advised[14,10]

If alpha-mannosidosis is suspected or a possibility, patients should be referred to a specialised centre for:

Acidic alpha-mannosidase activity assay

- The most efficient and reliable method of establishing a diagnosis[9]
- In affected individuals, acid alpha-mannosidase activity in peripheral blood leukocytes is 5–15% of normal activity[9]
- In carriers, acid α-mannosidase activity is ~40–60% of normal, and is therefore not a reliable method for carrier detection[9]

Molecular genetic testing

- Identification of disease-causing mutations in *MAN2B1* by molecular genetic testing can confirm the diagnosis and allow for family studies[14,9]
- This is carried out on DNA from peripheral blood cells, by polymerase chain reaction amplification followed by DNA sequencing[9]

Oligosaccharides in urine

- Elevated urinary excretion of oligosaccharides can be demonstrated by thin-layer chromatography or high-performance liquid chromatography[9]
- This test is suggestive of alpha-mannosidosis, but not diagnostic[9]

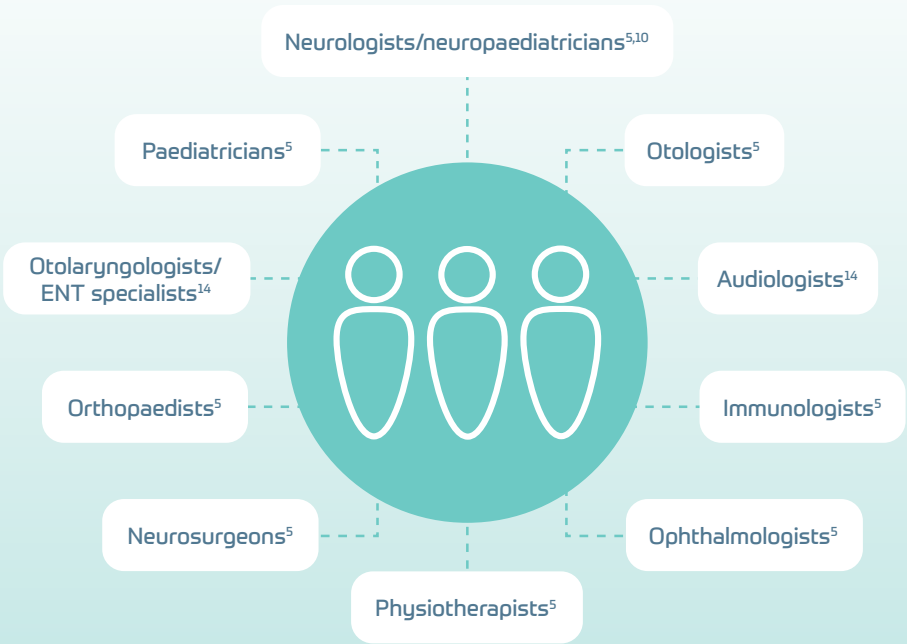
Peripheral blood examination

- In most affected individuals, microscopy demonstrates vacuoles in bone marrow smears and lymphocytes from peripheral blood[9]
- This is a useful screening test, but supplementary investigations are necessary[9]

The importance of multidisciplinary care

As alpha-mannosidosis affects multiple systems,[4,14] patients **should be managed by a multidisciplinary team (MDT)** to achieve diagnosis as early as possible, optimise quality of life and prevent complications related to disease progression.[5,10]

The MDT could involve, but is not limited to:[5,10,14]



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