



AN INTERACTIVE GUIDE TO THE UNDERDIAGNOSED AND UNDERESTIMATED BUT TREATABLE METABOLIC DISORDERS

Lysosomal Storage Disorders (LSDs) are more common than you might think but recognizing them can be difficult

Epidemiology

Individually
1: 50,000
1,000,000



Together
1: 7,000

Newborn screening programs find **5-80x** more cases than estimated



Late-onset or attenuated variants may not be recognized or diagnosed



Misdiagnosis is common



Missed diagnoses are also common



Variable presentation—in same family or even same genotype—makes diagnosis difficult

Barriers to recognition



Misdiagnosis is common and leads to diagnostic delays

Mean time to correct diagnosis after first symptoms in patients with Fabry Disease

13.7
Years



16.3
Years



Affected infants may appear healthy at first



Symptoms overlap with other disorders



LSD presentations are highly variable, even within the same family



Mild early symptoms may be present but not spotted



Family history may be misleading because of missing information, missed diagnoses or misdiagnoses, or the inheritance pattern

Identifying an LSD requires clinical recognition of red flags that implicate multi-system involvement



Look for clinical signs and symptoms of multi-organ symptom complexes



Apply consensus diagnostic algorithms in patients who have signs and symptoms that put an LSD in the differential diagnosis



Interpret newborn screening results (where available)

Treatments are available but must be started early

Enzyme Replacement Therapy (ERT)

Replaces the missing enzyme with a recombinant enzyme

1% to 5%
Amount of enzyme activity needed to correct deficiency



2
Recombinant enzyme is produced in cell culture and isolated



1
Enzyme is modified for cellular uptake and transport to lysosome



3
Patients receive weekly or monthly intravenous or intrathecal injections



4
Enzyme enters lysosome...



5
...and breaks down the accumulated substrate



In some LSDs, HSCCT can be used to replace the missing enzyme activity or may be the preferred approach



ERT does not reach all tissues equally, and does not cross the blood-brain barrier



Risk of anti-enzyme antibody response can reduce treatment effectiveness

Oral Chaperone Therapy (OCT)

Corrects the defect caused by some mutations



1
Some mutations affect the enzyme structure or trafficking, as well as its function

These proteins can be labeled for degradation or rescued by a chaperone



3
A chaperone stabilizes the enzyme structure, allowing proper trafficking and improved function



Small molecule chaperones may cross the blood brain barrier

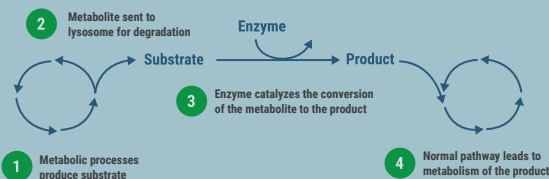


Only works for specific missense mutations (aka, "amenable mutations"), and never for deletions

Substrate Reduction Therapy (SRT)

Affects the upstream biochemical pathway to reduce production of the substrate before it can accumulate

Normal Metabolism



Disrupted Metabolism in LSDs

