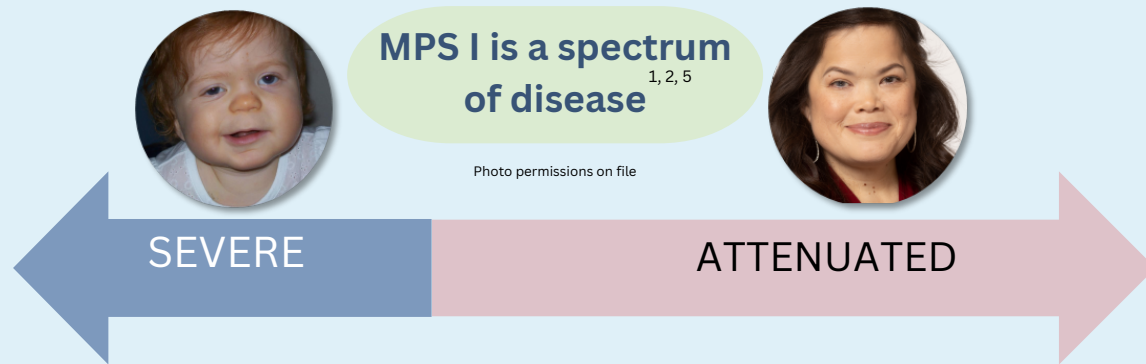


Mucopolysaccharidosis Type I (MPS I)

MPS I is a lysosomal storage disease that is due to a deficiency of lysosomal enzyme alpha-L-iduronidase which is caused by pathogenic variants in the *IDUA* gene. Alpha-L-iduronidase is needed to catabolize glycosaminoglycans (GAGs) in the lysosome. Reduced alpha-L-iduronidase activity results in the accumulation of GAGs, specifically heparan and dermatan sulfate.^{1, 2, 3, 4, 5, 6}

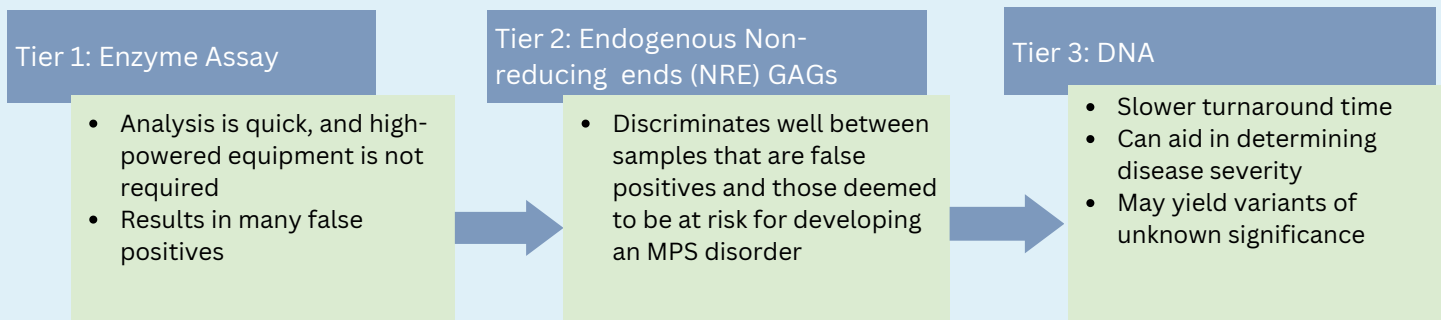


	Hurler	Hurler-Scheie	Scheie
Age at diagnosis	0.2 - 7 years	0.2 - 36 years	2 - 54 years
Effect on cognition	Pronounced mental delay with loss of acquired skills	No/mild mental delay; learning disabilities	No impairment
Mean life expectancy (without disease management)	7 years	Approximately 20 years	Adulthood
Phenotype distribution	~65%	~25%	~10%

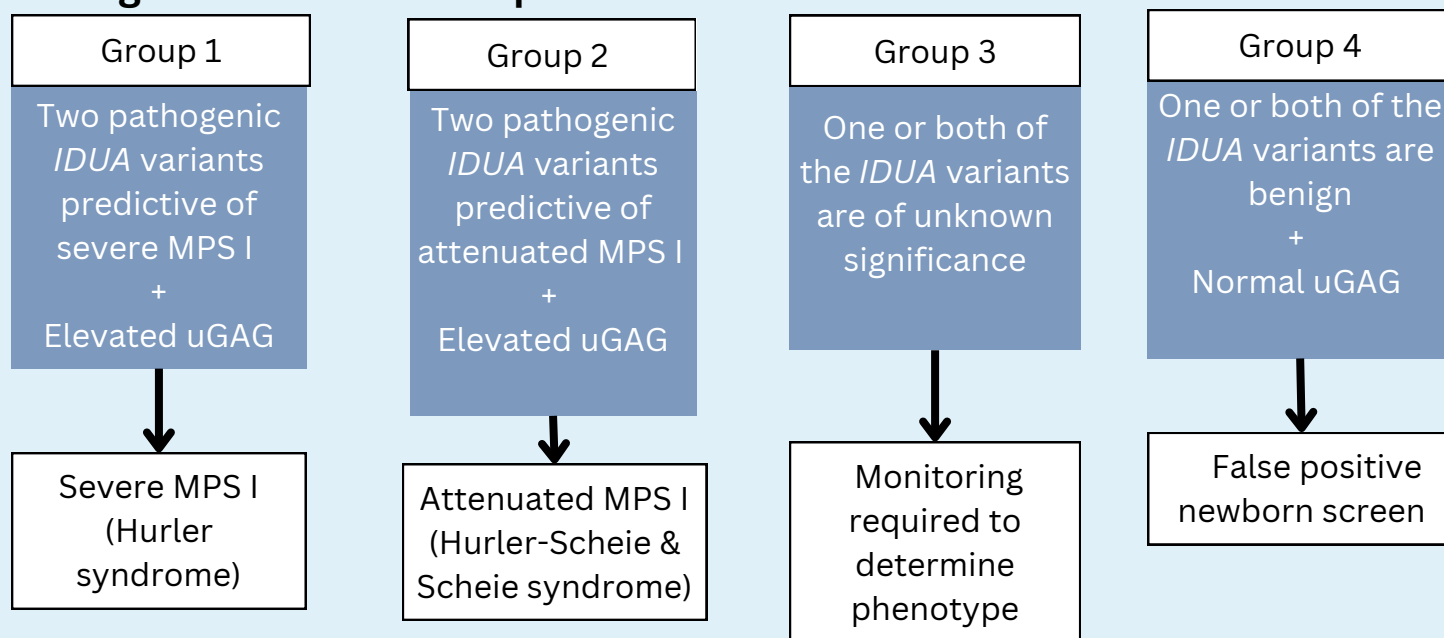
Clinical Manifestations of MPS I for Disease Severity Assessment^{1, 5, 7}

Assessments	Severe	Attenuated
Musculoskeletal	- Severity of dysostosis tends to correlate with disease severity; dysostosis on radiographs at birth possible - Gibbus deformity can be an early sign of severe disease	Later onset of skeletal abnormalities
Cardiac	- Early valvular disease - Cardiac involvement by echo is observed earlier than clinical symptoms - Mitral valvular disease most common - Rare cases of early endocardiofibroelastosis	Later onset of cardiac involvement compared to severe
Neurologic	- Early psychomotor development may be normal; developmental delay is obvious by 18 months - Signal alteration, enlarged perivascular spaces (PVS), ventriculomegaly are possible on imaging - Communicating high-pressure hydrocephalus is common	- Near normal or normal intellect - Signal alterations, enlarged PVS, ventriculomegaly and spinal stenosis are possible on imaging - Lower frequency of hydrocephalus early on, but may have insidious onset
Ophthalmological	Early corneal involvement may be observable by 6-7 weeks of age	Later onset of corneal clouding compared to severe
Respiratory	- Frequent upper respiratory tract infections before age 1 - Chronic recurrent rhinitis, copious nasal discharge without obvious infection - Sleep apnea common	- Rhinorrhea - Sleep apnea - Recurrent ear, nose, throat symptoms
Facial Dysmorphisms	Facial coarsening by age 2	Less obvious facial coarsening
Gastrointestinal	- Inguinal or umbilical hernias by age 1 are common - Hepatosplenomegaly is common	- Hernias in 65% with median onset by 3 years - Variable hepatosplenomegaly
Audiometry	Hearing loss is common and correlates with somatic disease severity	Moderate to severe hearing loss may develop

Recommended MPS I Newborn Screen Algorithm¹⁰



Algorithm for Follow up of Positive Newborn Screens for MPS I¹¹



Diagnosis

- Measuring alpha-L-iduronidase activity is the gold standard methodology for diagnosis⁵
- Alpha-L-iduronidase activity can be measured in leukocytes, plasma, serum, or dried blood spots
 - Diagnosis of MPS I can be confirmed by molecular analysis of the *IDUA* gene⁶
 - >100 disease-causing variants have been identified in the *IDUA* gene⁶
 - Homozygosity or compound heterozygosity for two severe variants always leads to severe disease⁶
 - Attenuated MPS I results from at least one *IDUA* missense allele which must confer residual *IDUA* enzyme activity⁶
 - Phenotype can be accurately predicted from the genotype for the majority of patients. However, predicting the phenotype from any genotype is not always possible due to unique pathogenic variants and imperfect *in silico* models⁶

Considerations⁸

- Anesthesia
 - Upper airway obstruction may cause difficulty with intubation
 - Risk increases with age
- Spinal instability
 - Careful positioning to avoid hyperextension of neck
 - Increased risk of complication with surgery

Genotype - Phenotype Correlations^{6,9}

Commonly Associated Severe Alleles

W402X / W402X
W402X / Q70X
Q70X / Q70X

Commonly Associated Attenuated Alleles

L490P / L490P
P533R / P533R
L238Q / W402X

Common Pseudodeficiency Alleles

c.235G>A (p.A79T)
c.246C>G (p.H82Q)

c.667G>A (p.D223N)
c.965T>A (p.V322E)

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