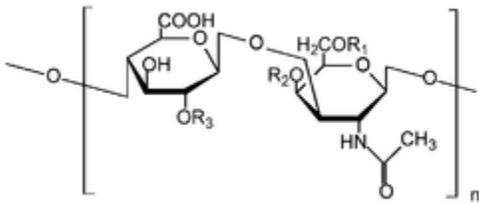
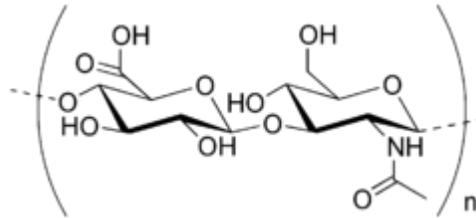


MUCOPOLYSACCHARIDES

Glycosaminoglycans (GAGs) or **mucopolysaccharides** are long unbranched polysaccharides consisting of a repeating disaccharide unit. GAGs are found throughout the body, often in mucus and in fluid around the joints. The repeating unit (except for keratan) consists of an amino sugar (N-acetylglucosamine or N-acetylgalactosamine) along with an uronic sugar (glucuronic acid or iduronic acid) or galactose.

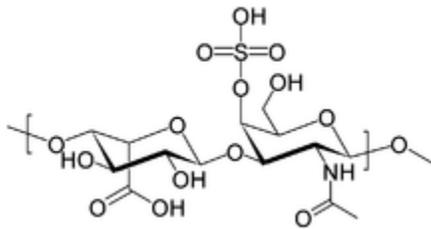


Chondroitin sulphate (Most prevalent GAG)

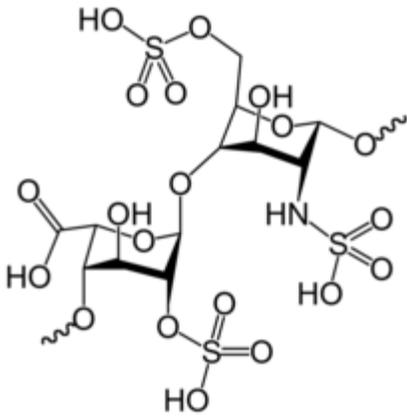


Hyaluronan

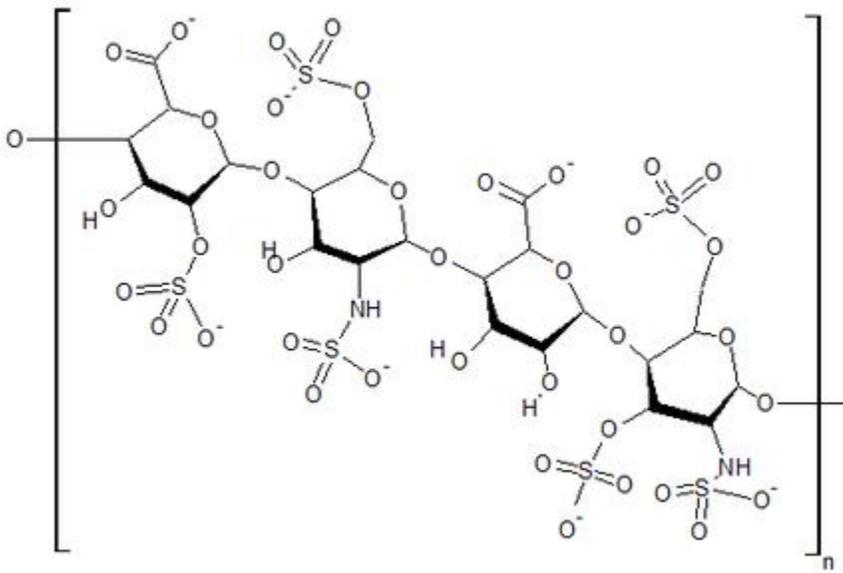
(The only GAG that is exclusively non-sulfated)



Dermatan sulphate



Heparin



Heparan sulphate

MUCOPLYSACCHARIDE METABOLIC DISORDERS

(SOURCE: <http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/84464>)

The mucopolysaccharidoses (MPSs) are a group of disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans: GAGs). Undegraded or partially degraded GAGs (also called mucopolysaccharides) are stored in lysosomes and excreted in the urine. Accumulation of GAGs in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in MPS disorders. There are 11 known enzyme deficiencies that result in MPSs. In addition, abnormal GAG storage is observed in multiple sulfatase deficiency and in I-cell disease. Finally, an abnormal excretion of GAGs in urine is observed occasionally in other disorders including active bone diseases, connective tissue disease, hypothyroidism, urinary dysfunction, and oligosaccharidoses.

MPSs are autosomal recessive disorders with the exception of MPS II, which follows an X-linked inheritance pattern. Affected individuals typically experience a period of normal growth and development followed by progressive disease involvement encompassing multiple systems. The severity and features vary, and may include facial coarsening, organomegaly, skeletal changes, cardiac abnormalities, and developmental delays. Moreover, disease presentation varies from as early as late infancy to adulthood.

A diagnostic workup for individuals with suspected MPS should begin with test MPSSC Mucopolysaccharides (MPS) Screen, Urine, which includes both the quantitative analysis of total GAGs and qualitative liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of the specific sulfates. Interpretation is based upon pattern recognition of the specific sulfates detected by MS/MS and the qualitative analysis of their relative amounts of excretion. However, an abnormal MPS analysis is not sufficient to conclusively establish a specific diagnosis. It is strongly recommended to seek confirmation by an independent method, typically in vitro enzyme assay (available in either blood or cultured fibroblasts from a skin biopsy) and/or molecular analysis.

After a specific diagnosis has been established, MPSQN / Mucopolysaccharides (MPS), Quantitative, Urine, which does not include the analysis of the specific sulfates, can be appropriate for monitoring the effectiveness of treatment, such as a bone marrow transplant or enzyme replacement therapy. However, some clinicians will opt to perform the MPS screen, which allows for monitoring of not only the total amount of GAGs, but also the excretion of specific sulfates, as these may change in patients with an MPS disorder undergoing treatment.

Table: Enzyme Defects and Excretion Products of Mucopolysaccharidoses

Disorder	Alias	Enzyme Deficiency (Mayo Medical Laboratories' Test, if applicable)	Sulfate(s) Excreted
MPS I	Hurler/Scheie	alpha-L-iduronidase (IDST)	DS/HS

MPS II	Hunter	Iduronate 2-sulfatase	DS/HS
MPS III A	Sanfilippo A	Heparan N-sulfatase	HS
MPS III B	Sanfilippo B	N-acetyl-alpha-D-glucosaminidase (ANAT, ANAS)	HS
MPS III C	Sanfilippo C	Acetyl-CoA:alpha-glucosaminide N-acetyltransferase	HS
MPS III D	Sanfilippo D	N-acetylglucosamine-6-sulfatase	HS
MPS IV A	Morquio A	Galactosamine-6-sulfatase (G6ST)	KS/C6S
MPS IV B	Morquio B	beta-galactosidase (BGAT, BGA)	KS
MPS VI	Maroteaux-Lamy	Arylsulfatase B (ARSB)	DS
MPS VII	Sly	beta-glucuronidase (BGLR)	DS/HS/C6S
MPS IX	Hyaluronidase deficiency	Hyaluronidase	None

KEY: C6S, chondroitin 6-sulfate; DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate

MPS I (Hurler/Scheie syndrome) is caused by a reduced or absent activity of the alpha-L-iduronidase enzyme. The incidence of MPS I is approximately 1 in 100,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy. This enzyme deficiency results in a wide range of clinical phenotypes that are further categorized into 3 phenotypes: MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), which cannot be distinguished via biochemical methods. Clinically, they are also referred to as MPS I and attenuated MPS I. MPS IH is the most severe and has an early onset consisting of skeletal deformities, coarse facial features, hepatosplenomegaly, macrocephaly, cardiomyopathy, hearing loss, macroglossia, and respiratory tract infections. Developmental delay is noticed as early as 12 months with death occurring usually before 10 years of age. MPS IH/S has an intermediate clinical presentation characterized by progressive skeletal symptoms called dysostosis multiplex. Individuals typically have little or no intellectual dysfunction. Corneal clouding, joint stiffness, deafness, and valvular heart disease can develop by early to mid-teens. Survival into adulthood is common. Cause of death usually results from cardiac complications or upper airway obstruction. Comparatively, MPS IS presents with the mildest phenotype. The onset occurs after 5 years of age. It is characterized by normal intelligence and stature; however, affected individuals do experience joint involvement, visual impairment, and obstructive airway disease.

MPS II (Hunter syndrome) is caused by a reduced or absent activity of the enzyme iduronate 2-sulfatase. The clinical features and severity of symptoms of MPS II are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, and profound neurologic involvement leading to developmental delays and

regression. The clinical presentation of MPS II is similar to that of MPS I with the notable difference of the lack of corneal clouding in MPS II. The inheritance pattern is X-linked and as such MPS II is observed almost exclusively in males with an estimated incidence of 1 in 170,000 male births. Symptomatic carrier females have been reported, but are very rare. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy.

MPS III (Sanfilippo syndrome) is caused by a reduced or absent activity of 1 of 4 enzymes (see Table above), resulting in a defect of heparan sulfate degradation. Patients with MPS III uniformly excrete heparan sulfate resulting in similar clinical phenotypes, and are further classified as type A, B, C, or D based upon the specific enzyme deficiency. Sanfilippo syndrome is characterized by severe central nervous system (CNS) degeneration, but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPSs. Onset of clinical features, most commonly behavioral problems and delayed development, usually occurs between 2 and 6 years in a child who previously appeared normal. Severe neurologic degeneration occurs in most patients by 6 to 10 years of age, accompanied by a rapid deterioration of social and adaptive skills. Death generally occurs by the 20s. The occurrence of MPS III varies by subtype with types A and B being the most common and types C and D being very rare. The collective incidence is approximately 1 in 58,000 live births.

MPS IVA (Morquio A syndrome) is caused by a reduced or absent N-acetylgalactosamine-6-sulfate sulfatase. Clinical features and severity of symptoms of MPS IVA are widely variable, but may include skeletal dysplasia, short stature, dental anomalies, corneal clouding, respiratory insufficiency, and cardiac disease. Intelligence is usually normal. Estimates of the incidence of MPS IVA syndrome range from 1 in 200,000 to 1 in 300,000 live births. Treatment with enzyme replacement therapy is available.

MPS IVB (Morquio B syndrome) is caused by a reduced or absent beta-galactosidase activity which gives rise to the physical manifestations of the disease. Clinical features and severity of symptoms of MPS IVB are widely variable ranging from severe disease to an attenuated form, which generally presents at a later onset with a milder clinical presentation. In general, symptoms may include coarse facies, short stature, enlarged liver and spleen, hoarse voice, stiff joints, cardiac disease, but no neurological involvement. The incidence of MPS IVB is estimated to be about 1 in 250,000 live births. Treatment options are limited to symptomatic management.

MPS VI (Maroteaux-Lamy syndrome) is caused by a deficiency of the enzyme arylsulfatase B. Clinical features and severity of symptoms are widely variable, but typically include short stature, dysostosis multiplex, facial dysmorphism, stiff joints, claw-hand deformities, carpal tunnel syndrome, hepatosplenomegaly, corneal clouding, and cardiac defects. Intelligence is usually normal. Estimates of the incidence of MPS VI range from 1 in 200,000 to 1 in 300,000 live births. Treatment options include hematopoietic stem cell transplantation and enzyme replacement therapy.

MPS VII (Sly syndrome) is caused by a deficiency of the enzyme beta-glucuronidase. The phenotype varies significantly from mild to severe presentations and may include macrocephaly, short stature,

dysostosis multiplex, hepatomegaly, coarse facies, and impairment of cognitive function. Likewise, the age of onset is variable ranging from prenatal to adulthood. MPS VII is extremely rare, affecting approximately 1 in 1,500,000 individuals.

MPS IX is a very rare disorder caused by a deficiency of the enzyme hyaluronidase. Patients present with short stature, flat nasal bridge, and joint findings. Urine GAGs are normal in MPS IX.

Multiple sulfatase deficiency (MSD) is an autosomal recessive disorder caused by mutations in the sulfatase-modifying factor-1 gene (*SUMF1*). Sulfatases undergo a common process that allows for normal expression of enzyme activity. Mutations in *SUMF1* impair that process, thereby resulting in decreased activity of all known sulfatase enzymes. Individuals with MSD have a complex clinical presentation encompassing features of each of the distinct enzyme deficiencies, including iduronate 2-sulfatase (MPS II), N-acetylgalactosamine-6-sulfate sulfatase (MPS IVA), arylsulfatase B (MPS VI), and arylsulfatase A (metachromatic leukodystrophy), steroid sulfatase (X-linked ichthyosis) and arylsulfatase F (chondrodysplasia punctata). MSD is extremely rare, affecting approximately 1 in 1,400,000 individuals.

Reference Values?

MPS, QUANTITATIVE

0-4 months: < or =53.0 mg/mmol creatinine
5-18 months: < or =31.0 mg/mmol creatinine
19 months-2 years: < or =24.0 mg/mmol creatinine
3-5 years: < or =16.0 mg/mmol creatinine
6-10 years: < or =12.0 mg/mmol creatinine
11-14 years: < or =10.0 mg/mmol creatinine
>14 years: < or =6.5 mg/mmol creatinine

MPS, QUALITATIVE

An interpretive report will be provided.

Interpretation?

An abnormally elevated excretion of glycosaminoglycans is characteristic of mucopolysaccharidoses.

The pattern of sulfates obtained by liquid chromatography-tandem mass spectrometry (LC-MS/MS) is usually characteristic of the enzyme deficiency.

When abnormal results are detected with characteristic patterns, a detailed interpretation is given, including an overview of the results and their significance, a correlation to available clinical information, elements of differential diagnosis, recommendations for additional biochemical testing, and in vitro confirmatory studies (enzyme assay and molecular test).

Cautions?

Occasionally, an abnormal value for total glycosaminoglycans (GAG) will be obtained on a specimen that yields a normal liquid chromatography-tandem mass spectrometry (LC-MS/MS) pattern. This situation can occur as an artifact when a patient is treated with low-molecular-weight heparin. Other known causes are sample contamination with acrylic polymers used in disposable diapers and several clinical situations associated with excessive connective tissue destruction, bladder disease, or bone disease.

Clinical Reference?

1. Neufeld EF, Muenzer J: The mucopolysaccharidoses. In *The Metabolic and Molecular Bases of Inherited Disease*. Eighth edition. Edited by CR Scriver, AL Beaudet, D Valle, et al. New York, McGraw-Hill Book Company, 2001, pp 3421-3452
2. Neufeld EF, Muenzer J: Chapter 136. The Mucopolysaccharidoses. In *Scriver's Online Metabolic and Molecular Bases of Inherited Disease*. Edited by D Valle, AL Beaudet, B Vogelstein, et al: McGraw Hill; 2013. Accessed July, 2013, Available at: <http://dx.doi.org/10.1036/ommbid.165>.