

## Overview

### Useful For

Supporting the biochemical diagnosis of one of the mucopolysaccharidoses: types I, II, III, IV, VI, or VII

### Genetics Test Information

This test is used to aid in the diagnosis and monitoring of patients with mucopolysaccharidoses (MPS) types I, II, III, IV, VI, and VII.

Accumulation of undegraded glycosaminoglycans (GAG; also known as mucopolysaccharides) leads to progressive cellular dysfunction and results in the typical clinical features seen with this group of disorders.

Dermatan sulfate (DS), heparan sulfate (HS), keratan sulfate (KS) and chondroitin-6-sulfate (C6S) are markers for a subset of MPS.

In urine:

- DS and HS are markers for MPS types I, II, III, VI and VII.
- KS is a marker for MPS IVA and MPS IVB.
- C6S is a marker for MPS IVA and MPS VII.

### Testing Algorithm

For more information see the following:

- [-Lysosomal Storage Disorders Diagnostic Algorithm, Part 1](#)
- [-Newborn Screening Follow up for Mucopolysaccharidosis type II](#)

If the patient has abnormal newborn screening result for mucopolysaccharidosis type I, immediate action should be taken. Refer to the appropriate American College of Medical Genetics and Genomics Newborn Screening ACT Sheet.(1)

### Special Instructions

- [Biochemical Genetics Patient Information](#)
- [Lysosomal Storage Disorders Diagnostic Algorithm, Part 1](#)
- [Newborn Screening Follow-up for Mucopolysaccharidosis type II](#)

### Highlights

Using liquid chromatography tandem mass spectrometry, this quantitative urine mucopolysaccharide screen provides analysis of the specific sulfates that are associated with at least 13 different disorders.

### Method Name

Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)

### NY State Available

Yes

## Specimen

### Specimen Type

Urine

### Ordering Guidance

This test alone is not appropriate for the diagnosis of a specific mucopolysaccharidosis (MPS). Follow-up enzymatic or molecular genetic testing must be performed to confirm a diagnosis of an MPS.

### Necessary Information

1. Patient's age is required.
2. Reason for testing is required.
3. [Biochemical Genetics Patient Information](#) (T602) is recommended. This information aids in providing a more thorough interpretation of results. Send information with specimen.

### Specimen Required

**Patient Preparation:** Do not administer low-molecular weight heparin prior to collection

**Supplies:** Sarstedt Aliquot Tube, 5 mL (T914)

**Container/Tube:** Plastic, 5-mL urine tube

**Specimen Volume:** 2 mL

**Pediatric Volume:** 1 mL

**Collection Instructions:** Collect a random urine specimen (**early morning preferred**).

### Forms

1. [Biochemical Genetics Patient Information](#) (T602)
2. If not ordering electronically, complete, print, and send a [Biochemical Genetics Test Request](#) (T798) with the specimen.

### Specimen Minimum Volume

1 mL

### Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

### Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Urine	Refrigerated (preferred)	90 days	
	Frozen	365 days	
	Ambient	7 days	

## Clinical & Interpretive

### Clinical Information

The mucopolysaccharidoses 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-6-sulfate, which are collectively called glycosaminoglycans (GAG). Undegraded or partially degraded GAG are stored in lysosomes and excreted in the urine. Accumulation of GAG in lysosomes interferes with normal functioning of cells, tissues, and organs resulting in the clinical features observed in mucopolysaccharidosis (MPS) disorders. There are 11 known enzyme deficiencies that result in the accumulation of GAG. In addition, abnormal GAG storage is observed in multiple sulfatase deficiency and in I-cell disease. Finally, abnormal excretion of GAG in urine is observed occasionally in other disorders including active bone diseases, connective tissue disease, hypothyroidism, urinary dysfunction, and oligosaccharidoses.

Mucopolysaccharidoses are autosomal recessive disorders except for 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 this test, which includes the quantitative liquid chromatography tandem mass spectrometry (LC-MS/MS) analysis of the specific sulfates or GAG. Interpretation is based upon pattern recognition of the specific sulfates detected by MS/MS and the quantitative analysis of their amounts of excretion. However, an abnormal mucopolysaccharide 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) or molecular analysis.

After a specific diagnosis has been established, this test can be appropriate for monitoring the effectiveness of treatment, such as a bone marrow transplant or enzyme replacement therapy (ERT). This test allows for monitoring of 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	Sulfates excreted
MPS I	Hurler/Scheie	Alpha-L-iduronidase	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	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	KS/C6S
MPS IV B	Morquio B	Beta-galactosidase	KS
MPS VI	Maroteaux-Lamy	Arylsulfatase B	DS

MPS VII	Sly	Beta-glucuronidase	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 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 main types: MPS IH (Hurler syndrome), MPS IS (Scheie syndrome), and MPS IH/S (Hurler-Scheie syndrome), which are not typically distinguishable 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 of age, with death occurring usually before 10 years of age when left untreated. 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-adolescence. 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 male patients with an estimated incidence of 1 in 170,000 male births. Female patients who are symptomatic carriers are very rare but have been reported. Treatment options include hematopoietic stem cell transplantation and ERT.

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. MPS III is characterized by severe central nervous system (CNS) degeneration but only mild physical disease. Such disproportionate involvement of the CNS is unique among the MPS. 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 third decade of life (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. Treatment options are limited to symptomatic management.

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,

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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 ERT 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 ERT.

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. Treatment options include hematopoietic stem cell transplantation and ERT.

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 GAG are normal in MPS IX.

**Reference Values****DERMATAN SULFATE**

< or =1.00 mg/mmol creatinine

**HEPARAN SULFATE**

< or =4 years: < or =0.50 mg/mmol creatinine

> or =5 years: < or =0.25 mg/mmol creatinine

**CHONDROITIN-6 SULFATE**

< or =24 months: < or =10.00 mg/mmol creatinine

25 months-10 years: < or =2.50 mg/mmol creatinine

> or =11 years: < or =1.50 mg/mmol creatinine

**KERATAN SULFATE**

< or =12 months: < or =2.00 mg/mmol creatinine

13-24 months: < or =1.50 mg/mmol creatinine

25 months-4 years: < or =1.00 mg/mmol creatinine

5-18 years: < or =0.50 mg/mmol creatinine

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> or =19 years: < or =0.30 mg/mmol creatinine

**Interpretation**

Elevations of dermatan sulfate, heparan sulfate, keratan sulfate, and/or chondroitin-6-sulfate may be indicative of one of the mucopolysaccharidoses types I, II, III, IV, VI, or VII.

Elevations of any or all sulfate species may be indicative of multiple sulfatase deficiency or mucopolipidosis II/III.

Rarely, an elevation of keratan sulfate may be indicative of alpha-fucosidosis.

**Cautions**

No significant cautionary statements

**Clinical Reference**

1. Newborn Screening ACT Sheet [alpha-L-iduronidase deficiency with or without glycosaminoglycan (GAG) accumulation] Mucopolysaccharidosis Type I (MPS I). American College of Medical Genetics and Genomics; 2023. Updated November 2023. Accessed June 10, 2024. Available at [www.acmg.net/PDFLibrary/MPSI-ACT-Sheet.pdf](http://www.acmg.net/PDFLibrary/MPSI-ACT-Sheet.pdf)
2. de Ru MH, van der Tol L, van Vlies N, et al. Plasma and urinary levels of dermatan sulfate and heparan sulfate derived disaccharides after long-term enzyme replacement (ERT) in MPS I: correlation with the timing of ERT and with total urinary excretion of glycosaminoglycans. *J Inherit Metab Dis.* 2013;36(2):247-255
3. Neufeld EF, Muenzer J: The mucopolysaccharidoses. In: Valle DL, Antonarakis S, Ballabio A, Beaudet AL, Mitchell GA, eds. *The Online Metabolic and Molecular Bases of Inherited Disease.* McGraw Hill; 2019. Accessed November 29, 2023. Available at <https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225544161>
4. Puckett Y, Mallorga-Hernandez A, Montano AM. Epidemiology of mucopolysaccharidoses (MPS) in the United States: challenges and opportunities. *Orphanet J Rare Dis.* 2021;16(1):241
5. Freeze HH. Genetic disorders of glycan degradation. In: Varki A, Cummings RD, Esko JD, et al, eds. *Essentials of Glycobiology.* 2nd ed. Cold Spring Harbor Laboratory Press; 2009. Accessed November 29, 2023. Available at [www.ncbi.nlm.nih.gov/books/NBK1934/](http://www.ncbi.nlm.nih.gov/books/NBK1934/)

**Performance****Method Description**

Dermatan sulfate (DS), heparin sulfate (HS), keratan sulfate (KS) and chondroitin-6-sulfate (C6S) are enzymatically digested from urine. The reaction mixture is centrifuged and analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS). The ratio of the extracted peak area of DS, HS, KS and C6S to internal standard as determined by LC-MS/MS is used to calculate the concentration of DS, HS, KS and C6S in the sample.(Unpublished Mayo method)

**PDF Report**

No

**Day(s) Performed**

Monday

## Report Available

8 to 15 days

## Specimen Retention Time

1 month

## Performing Laboratory Location

Rochester

## Fees & Codes

### Fees

- Authorized users can sign in to [Test Prices](#) for detailed fee information.
- Clients without access to Test Prices can contact [Customer Service](#) 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact [Customer Service](#).

### Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

### CPT Code Information

83864

82570

### LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
MPSQU	Mucopolysaccharides Quant, U	94691-3

Result ID	Test Result Name	Result LOINC® Value
BG716	Reason for Referral	42349-1
605986	Dermatan Sulfate	94692-1
605987	Heparan Sulfate	94693-9
605988	Chondroitin-6 Sulfate	94690-5
605989	Keratan Sulfate	92806-9
605990	Interpretation	59462-2
605985	Reviewed By	18771-6