Mucopolysaccharidosis (MPS I)

Overview

Mucopolysaccharidosis I (MPS I) is an inherited, multisystem, progressive disorder caused by a deficiency of the lysosomal enzyme α-L-iduronidase, leading to a buildup of its major substrates, the glycosaminoglycans (GAGs) dermatan and heparan sulfate resulting in developmental delay and regression, plus respiratory, cardiac, and musculoskeletal dysfunction.[1] MPS I is caused by mutations in the *IDUA* gene responsible for producing α-L-iduronidase.[2] Symptoms of MPS I range over a continuum of severity, with a variable age of onset, progression, and organ involvement[1]. There is considerable phenotypic overlap among several MPS disorders.

Severe MPS I (historically called Hurler syndrome)[2]:
- Mean age of diagnosis is 9 months
- Infants often appear normal at birth
- Severe developmental delay, regression, and severe somatic multi-organ complications become apparent after birth
- Death occurs within the first 10 years of life

Attenuated MPS I (historically called Hurler-Scheie and Scheie syndromes)[2]:
- Onset of symptoms occurs between 3-10 years of age
- Patients are developmentally normal at 2 years of age, and may develop learning disabilities
- Moderate somatic involvement
- Rate of disease progression ranges from death in the second to third decade of life to a normal life span with significant disease burden

Incidence

- Severe MPS I occurs in approximately 1 in 100 000 newborns[2,3]

Inheritance

- Autosomal recessive disorder caused by pathogenic variants in both copies of the *IDUA* gene[2]

Diagnosis

Definitive diagnosis is established by:

- α-L-iduronidase enzyme activity assay: demonstrating absence or deficiency (does not allow for differentiation between severe and attenuated)[2]
- *IDUA* gene sequencing: demonstrating two pathogenic variants in *trans* (one from each parent). Though identification of pathogenic variants is not required for diagnosis, it can provide secondary confirmation and important information related to phenotype[2]

The following evaluations may support a diagnosis of MPS I:

Clinical Findings

- Children will have coarse facial features, early frequent upper-respiratory infections (including otitis media), inguinal or umbilical hernia, developmental delay and regression[2]
- Both children and adults will have hepatosplenomegaly, joint stiffness, limited range of motion, joint contractures, carpal tunnel, and corneal clouding[2]

Laboratory Testing

- Blood or urine GAGs: Typically elevated in all MPS disorders, but can be normal in attenuated forms or with dilute urine samples[2]
- Individual GAGs: Elevated heparan sulfate and dermatan sulfate are characteristic of MPS I (and MPS II)[2]
  - Non-reducing ends can differentiate between MPS I and MPS II

Other

- Skeletal assessment: Dysostosis multiplex, scoliosis, kyphosis, hip dysplasia, vertebral beaking, phalangeal tapering, carpal tunnel, pes cavus, and genu valgum[1]
- Ophthalmologic assessments: corneal clouding, glaucoma, retinopathy, optic neuropathy[5]
- Echocardiogram/ECG: Mitral and aortic regurgitation (valve involvement is universal in severe MPS I; mitral is most common). Cardiomyopathy, arrhythmia, coronary artery disease can be seen[1]
- MRI/CT/US abdomen: hepatosplenomegaly can be seen in both severe and attenuated MPS I[1]

Testing Options for MPS I

Some of the laboratories offering testing for both MPS I enzyme assay (α-L-iduronidase) and *IDUA* sequencing. There may be other testing appropriate for your patient, and this is not an endorsement of any specific laboratory. Other testing options can be found at www.concertgenetics.com or www.ncbi.nlm.nih.gov/gtr. Consult each laboratory for a full range of options. Content is current at time of publication, and tests may not be available in all states; please call laboratory to confirm test availability, sample shipping information, and all other logistics. Sanofi does not review or control the content of non-Sanofi websites. This listing does not constitute an endorsement by Sanofi of information provided by any other organizations.

Laboratory	Available Testing	Sample Requirements	Avg TAT
ARUP Laboratories	Enzyme	WB: 1-3 ml EDTA (lavender) tube or ACD (yellow) tube	3-10 d
	GAGs	10-20 ml first morning urine, frozen	4-14 d
Centogene	Enzyme	WB: 1 ml EDTA (lavender) tube; DBS card: 10 circles	7 d
	IDUA Sequencing	WB: 1 ml EDTA (lavender) tube; DBS card: 10 circles; Saliva; Buccal swab	15-25 d
Duke University	Enzyme	WB: 4 ml EDTA (lavender) tube; DBS card: 5 circles	15 d
	IDUA Sequencing	WB: 2-3 ml EDTA (lavender) tube; DBS card: 5 circles	28 d
	GAGs	1 ml random urine, frozen	21 d
Greenwood Genetic Center	Enzyme	WB: 5-10 ml sodium heparin (green) tube; Plasma; DBS card: 3 circles	2 wks
	IDUA Sequencing	WB: 5-6 mL EDTA (lavender) tube; DBS card: 3 circles; Saliva	3 wks
	Qual/Quant GAGs	3 ml random urine, frozen	14 d
Mayo Clinic Laboratories	Enzyme	WB: 2 ml EDTA (lavender) or ACD (yellow) tube; DBS card: 2 circles	8-15 d
	IDUA Sequencing	WB: 3 ml EDTA (lavender) or ACD (yellow) tube; DBS card: 2-5 circles	14-20 d
	GAGs	WB: 2ml EDTA (lavender) tube; Serum; DBS card: 2 circles; 3 ml first void frozen	2-5 d
Revvity Omics	Enzyme	WB: 2-5 ml EDTA (lavender) tube; DBS card: 6 circles	3 d
	IDUA Sequencing	WB: 2-5 ml EDTA (lavender) tube; DBS card: 6 circles; Saliva	3-5 wks
Seattle Children's	Enzyme	WB: 6-10 ml ACD (yellow) tube or heparin (green) tube	7-10 d
	GAGs	1-2 ml urine sterile screw-capped container/tube	7 d
The Lantern Project (Revvity Omics)	Enzyme	WB: 2-10 ml EDTA (lavender) tube; DBS card: 3 circles	3 d
	IDUA Sequencing (incl Del/Dup)	WB: 2-10 ml EDTA (lavender) tube; DBS card: 3 circles; Saliva(per Oragene kit)	3 wks
	MPS 7 Enzyme Panel	WB: 2-10 ml EDTA (lavender) tube (volume varies with age); DBS card: 3 circles	3 wks

Laboratory	Kits	Mobile Phlebotomy	Billing	Contact
ARUP Laboratories	No	No	Inst	P: 800-522-2787 E: clientservices@aruplab.com W: www.aruplab.com
Centogene	Blood, DBS, Saliva	Yes	Inst, Self-pay, Ins	P: 617-580-2102 E: customer.support-US@centogene.com W: www.centogene.com
Duke University	No	No	Inst	P: 919-613-8400 E: clientservices@dm.duke.edu W: https://testcatalog.duke.edu
Greenwood Genetic Center	Blood, DBS, Saliva	No	Inst, Self-pay, Ins (SC residents only)	P: 800-473-9411 E: labgc@ggc.org W: www.ggc.org
Mayo Clinic Laboratories	DBS (in some cases)	Yes	Inst (ins can be billed in some cases, Inst account required)	P: 800-533-1710 E: mcl@mayo.edu W: www.mayocliniclabs.com
Revvity Omics (including The Lantern Project*)	Blood, DBS, Saliva	No	Inst, Self-pay, No charge*	P: 866-354-2910 E: genomics@revvity.com W: www.revvity.com W: www.LanternProjectDx.com
Seattle Children's Hospital Laboratory	No	No	Inst, Self-pay, Ins	P: 206-987-2216 E: labclientservices@seattlechildrens.org W: https://seattlechildrenslab.testcatalog.org/

***Testing is performed at no charge; local charges may apply for sample collection, processing, or shipping.**

avg TAT = average turnaround time; d = days; DBS = dried blood spot; del = deletion; dup = duplication analysis; incl = including; Ins = insurance; Inst = institution; min = minimum; WB = whole blood; wks = weeks.

References: 1. Arn P, et al. *J Pediatr.* 2009; 154:859-64 e3. **2.** Clarke LA. NCBI Bookshelf, a service of the National Library of Medicine, National Institutes of Health (NIH). Available at: https://www.ncbi.nlm.nih.gov/books/NBK1162/. Accessed June 1, 2024. **3.** Beck M, et al. *Genet in Med.* 2014;16(10):759. **4.** Muenzer J, et al. Mucopolysaccharidosis I: management and treatment guidelines. ***Pediatrics.*** 2009;123(1):19-29. doi:10.1542/peds.2008-0416. **5.** Tomatsu S, et al. J Clin Med. 2019;8(9):1467.

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