MPS I Biomarker: Glycosaminoglycans (GAGs)

Disease Overview

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

Glycosaminoglycans

GAGs are located on the cell surface and by attaching to proteins, turn into proteoglycans or other constituents of extracellular matrix.[3]

- GAGs can be measured in urine and blood.[4,5]

Quantitative total urine GAG measurement has been used as a tool in the diagnostic algorithm for MPS I, but total GAG analysis alone cannot conclusively establish a diagnosis.[4] Furthermore, there is insufficient evidence to establish a correlation between GAG levels and phenotype.

- Traditionally, total urine GAGs have been measured using a dye-binding assay. This method cannot be used with blood samples.[5]
- Now, mass spectrometry has largely replaced the dye-binding assay due to its increased sensitivity and specificity to detect various molecular species.[6]
- Mass spectrometry can be used to quantify GAGs in whole blood, DBS and urine.[7]

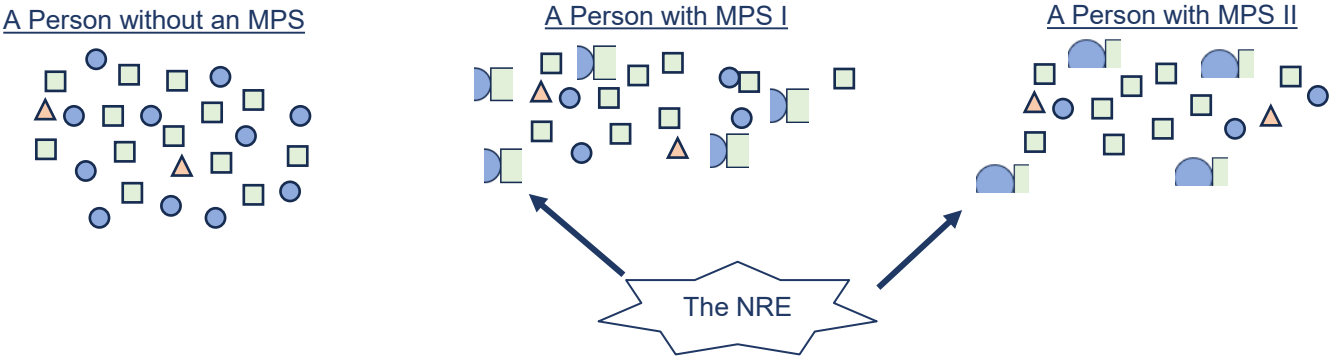
Blood GAGs are performed either using traditional MS/MS analysis or non-reducing end analysis, and can be used:

- to monitor MPS I disease burden.[8]
- as a biomarker of efficacy following hematopoietic stem cell transplantation.[9]
- as a second-tier test in newborn screen (NBS) to reduce the number of false positives.[6]

Non-reducing Ends (NRE)

Non-reducing ends (NRE) are unique glycan structures that are typically only present in samples from individuals affected with MPS. This is how they form:[10]

Enzymes degrade the GAGs *in vivo*



Laboratory specialists are able to isolate the non-reducing end with certain techniques. Each NRE is specific to it's associated MPS. Therefore, the NRE found in a person with MPS I is not expected to be found in a person with a different MPS subtype.

Recommended MPS Newborn Screening Algorithm[11]

Tier 1: Enzyme Assay

- Analysis is quick, and high-powered equipment is not required
- Results in many false positives[10]

Tier 2: Endogenous NRE GAGs

- Discriminates well between samples that are false positives and those deemed to be at risk for developing an MPS disorder[10]

Tier 3: DNA

- Slower turn around time
- Can aid in determining disease severity[12]
- May yield variants of unknown significance[10]

Clinician Considerations

- GAG testing is part of the screening process for MPS and elevated GAGs alone are not sufficient to diagnose MPS in an individual.[4]
- It not recommended to compare GAG results between different reference laboratories due to different methodologies, lack of internal reference standards, and lack of standardized reagents.[7]
- GAG levels are age-dependent.[5]

GAGs Testing Options

Sanofi does not review or control the content of non-Sanofi websites. These listings do not constitute an endorsement by Sanofi of information provided by any other organizations. The following is a selection of laboratories offering GAG testing. This is not an exhaustive list of labs that offer one or the other or an endorsement of any one lab. Other testing options can be found at www.concertgenetics.com or www.ncbi.nlm.nih.gov/gtr. To test individuals for an MPS disorder, please contact your lab of choice to discuss. Content is current at time of printing and tests may not be available in all states; please call laboratory to confirm test availability, sample shipping information, and all other logistics.

Lab	Test Name	Specimen	Method	TAT	Billing	Contact
ARUP	MPS Screen (0081357)	20 mL urine	Quant. GAGs	4-14 d	Inst, Self-Pay, Ins	P: 1-800-522-2787 E: clientservices@aruplab.com W: www.aruplab.com
	MPS I/II NRE (3003552)	2 mL urine	NRE	14-21 d		
	MPS I/II NRE (3003566)	500 µL serum or plasma	NRE	14-21 d		
Duke Biochemical Genetics Laboratory	MPS GAGs (LAB9484)	1 mL urine	Quant. GAGs (excludes KS)	21 d	Inst	P: 919-549-0445 W: https://clinlabs.duke.edu/biochemical-genetics-laboratory
	MPS GAG Screen (LAB9534)	1 mL urine	Quant. GAGs (includes KS)	21 d		
Greenwood Genetic Laboratory	MPS Urine Analysis	3 mL urine	Quant. GAGs	14 d	Inst, Ins (SC residents only), Self-pay	P: 800-473-9411 E: labgc@ggc.org W: www.ggc.org
	MPS I/II Urine Monitoring	3 mL urine	Quant. GAGs (Total GAGs, DS, HS)	10 d		
Mayo Medical Laboratories	MPSBS	DBS card	Quant. GAGs	3-5 d	Inst (Ins can be billed in some cases)	P: 507-284-1759 E: mcl@mayo.edu W: www.mayocliniclabs.com
	MPSER	0.5 mL serum	Quant. GAGs	9-15 d		
	MPSQU	2 mL urine	Quant. GAGs	8-15 d		
	MPSWB	2 mL WB	Quant. GAGs	3-5 d		
Revvity Omics	MPS I Marker (BG101)	DBS card	NRE - Endogenous	7 d	Inst, Self-Pay	P: 866-354-2910 E: genomics@revvity.com W: www.revvity.com

d=day; DBS=dried blood spot; DS=dermatan sulfate; Ins=insurance; Inst=institutional; HS=heraran sulfate; KS=keratin sulfate; MS/MS=liquid chromatography tandem mass spectrometry; Quant. GAGs=quantitative glycosaminoglycans; TAT=turn around time; WB=whole blood

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