
# CLUSTERS OF MPS IN LATIN AMERICA

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# DISCLOSURES

- I have been in receipt of honoraria for lectures on LSDs from Sanofi-Genzyme Corp
- Lucid and Biomarin consultant
- Informed consent was obtained for image use

# OUTLINE

- MPS introduction
- GAGs
- MPS management
- Clusters of MPS in Latin America

# MUCOPOLYSACCHARIDOSES

- Mucopolysaccharidoses (MPS) are rare lysosomal storage disorders caused by deficiency of lysosomal hydrolases leading to the accumulation of undegraded glycosaminoglycans (GAGs) (Table I). With the exception of MPS II, which is X-linked, the MPS are autosomal recessive.

**Table I** – Classification of the MPS approached in this study

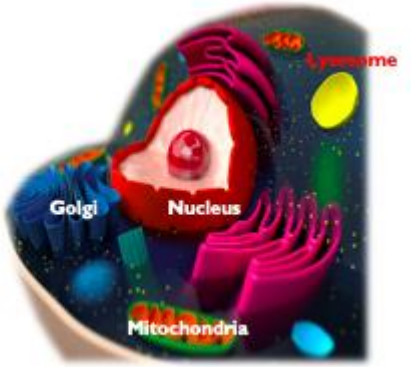
| Number | Enzyme deficiency | Eponym | Storage material | Gene |
|---|---|---|---|---|
| IIIB | α-N-acetylglucosaminidase | Sanfilippo B | Heparan sulfate | *NAGLU* |
| IIIC | Acetyl-coA-α-glucosaminide acetyltransferase | Sanfilippo C | Heparan sulfate | *HGSNAT* |
| IVA | N-acetylgalactosamine-6-sulfate sulfatase | Morquio A | Chondroitin-6-sulfate & Keratan sulfate | *GALNS* |
| VI | N-acetylgalactosamine-4-sulfatase | Maroteaux-Lamy | Dermatan sulfate | *ARSB* |

# GLYCOSAMINOGLYCANS (GAGS) ARE IMPORTANT FOR CELLULAR FUNCTION

- Gags are important structural components of cellular membranes, extracellular matrix, connective tissue, and joint fluids

- At the cellular level, GAGs are involved in cell division, differentiation, and cell-cell communication

- In healthy individuals, GAGs are degraded by lysosomal enzymes in a stepwise fashion within the lysosome



# GLYCOSAMINOGLYCANS- GAGS

| Category | Uronic acid | Hexosamine | Modifications |
|---|---|---|---|
| Heparin/heparan | Iduronic acid/glucuronic acid | Glucosamine | X-sulfated<br>Y-acetylated/sulfated |
| Chondroitin/ dermatan | Iduronic acid/glucuronic acid | Galactosamine | X-sulfated |
| Keratan | Galactose | Glucosamine | X-sulfated |
| Hyaluronic acid | Glucuronic acid | Glucosamine | None |

Sasisekharan et al., 2006

# GAG- SUB CLASSES

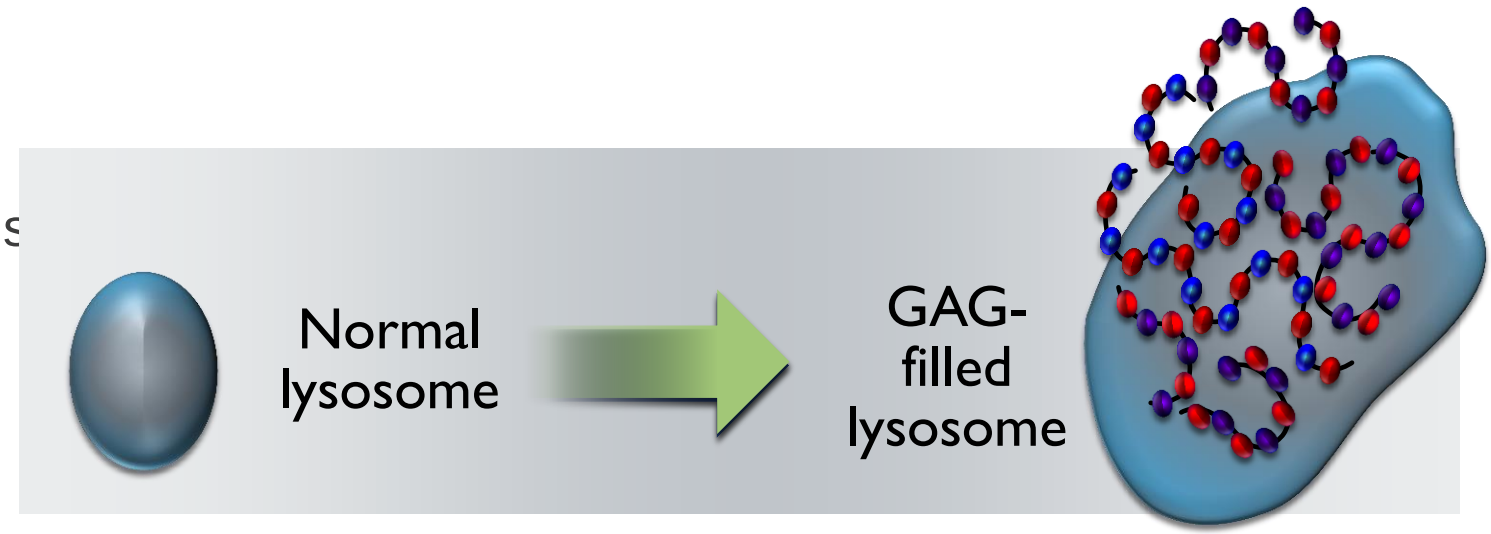
| Category | Modifications | Subclasses |
|---|---|---|
| Heparan | X-sulfated Y-acetylated/sulfated | **HS-0S, HS-NS,** HS-6S, HS-triS, HS-diS1 |
| Chondroitin/ dermatan | X-sulfated | **C4S, C6S, DS** |
| Keratan | X-sulfated | **Di-KS, Mono-KS** |

CS= chondroitin sulfate
Di-KS= di-sulfated keratan sulfate
DS= dermatan sulfate
HS= heparan sulfate
Mono-KS= mono-keratan sulfate

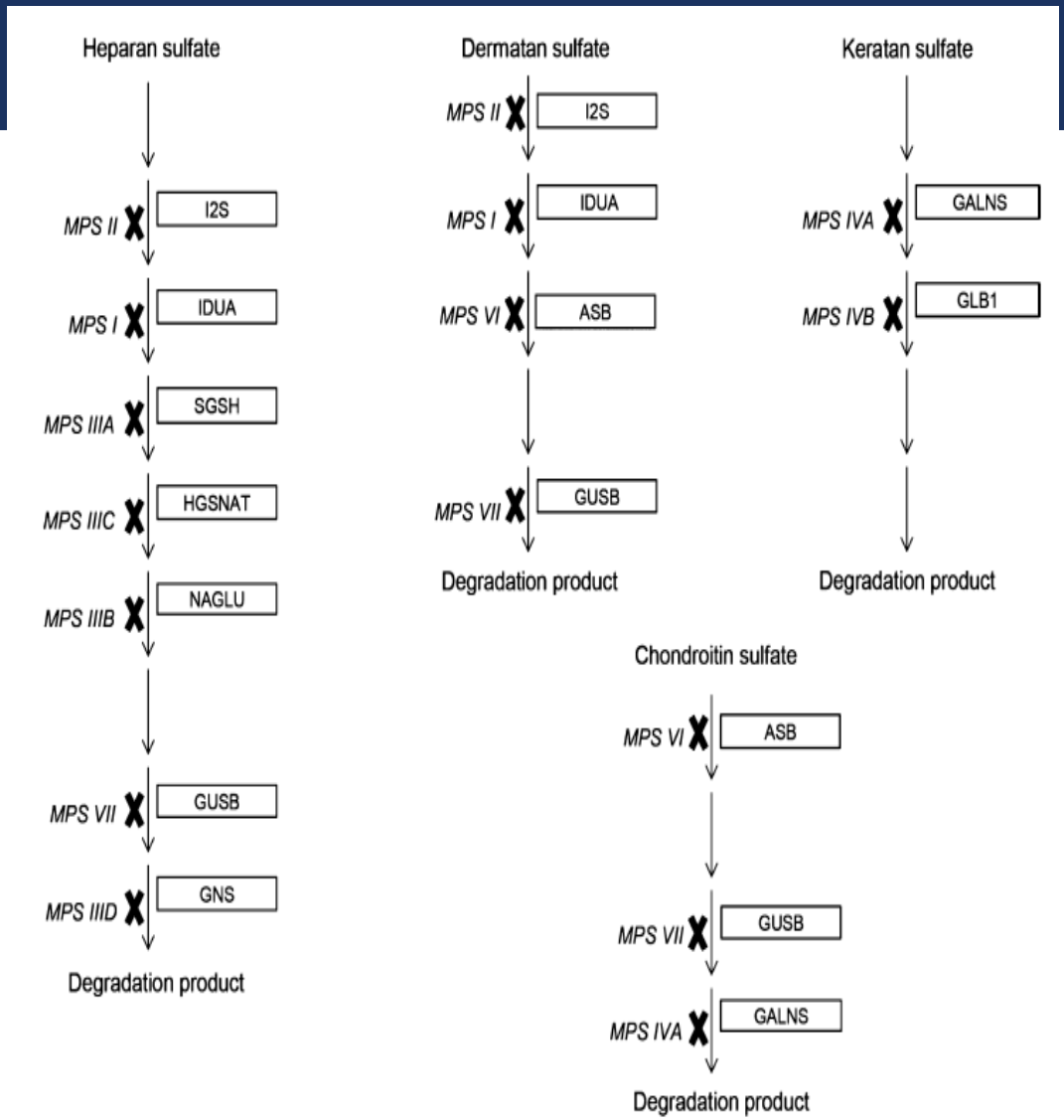
Sasisekharan et al., 2006

# PATHOPHYSIOLOGY MUCOPOLYSACCHARIDOSES

- Patients with mutations in genes coding for lysosomal enzymes
- Thus



# Impaired GAG catabolism leading to MPSs




Noh et al., 2014

# MPS: BURDEN OF DISEASE

## Patients

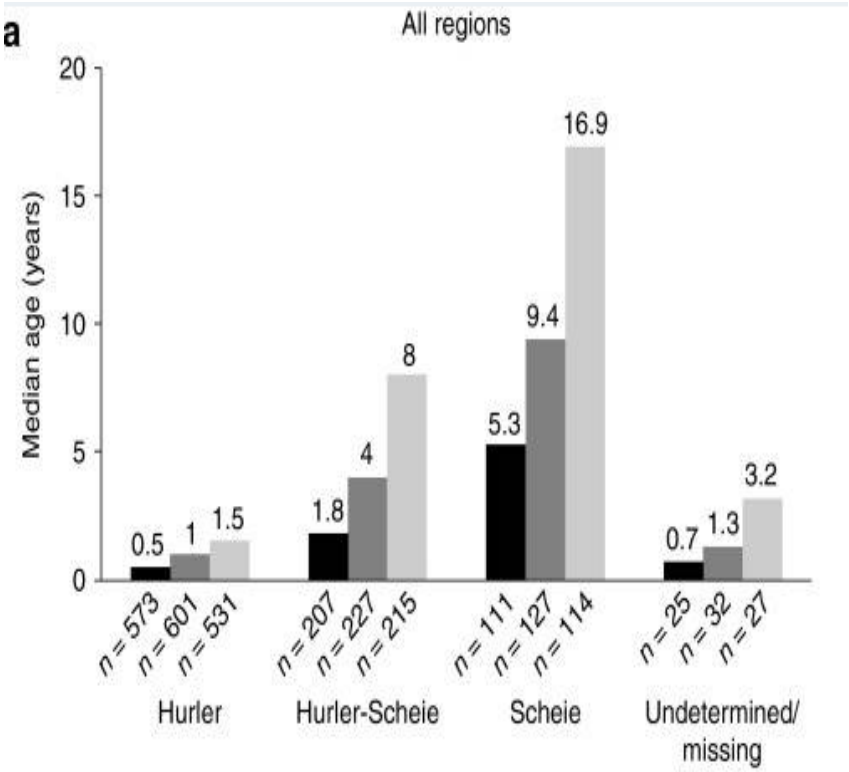
- GAG accumulation occurs systemically and can result in widespread tissue damage[1]
  - Tissue damage is progressive and may be irreversible in some areas of the body[1,2]
  - Widespread pain, decreased mobility, and decreased respiratory function affect the patient's quality of life[3]
- Most patients with attenuated forms of MPS are able to receive mainstream education[1]
  - Patients with severe forms of MPS experience developmental delay and cognitive decline[4]

## Caregivers

- Diagnosis can be obtained by pediatricians or primary care physicians, whereas symptom management often requires multispecialty care[4]
- As mobility decreases, patients may become more dependent on caregivers to assist them with daily activities[1]
- Home adaptations may be required for an affected child[1]

**1**. National MPS Society. A guide to understanding MPS I. http://mpssociety.org/wp-content/uploads/2011/07/booklet_MPS_I_v8.pdf. 2008. **2**. Neufeld et al. 2001 **3**. Wraith JE. 2005; **4**. Muenzer J, et al. *2009*

# SYMPTOM ONSET AND DIAGNOSIS TIMELINE




The delay in diagnosis may result in delayed disease management

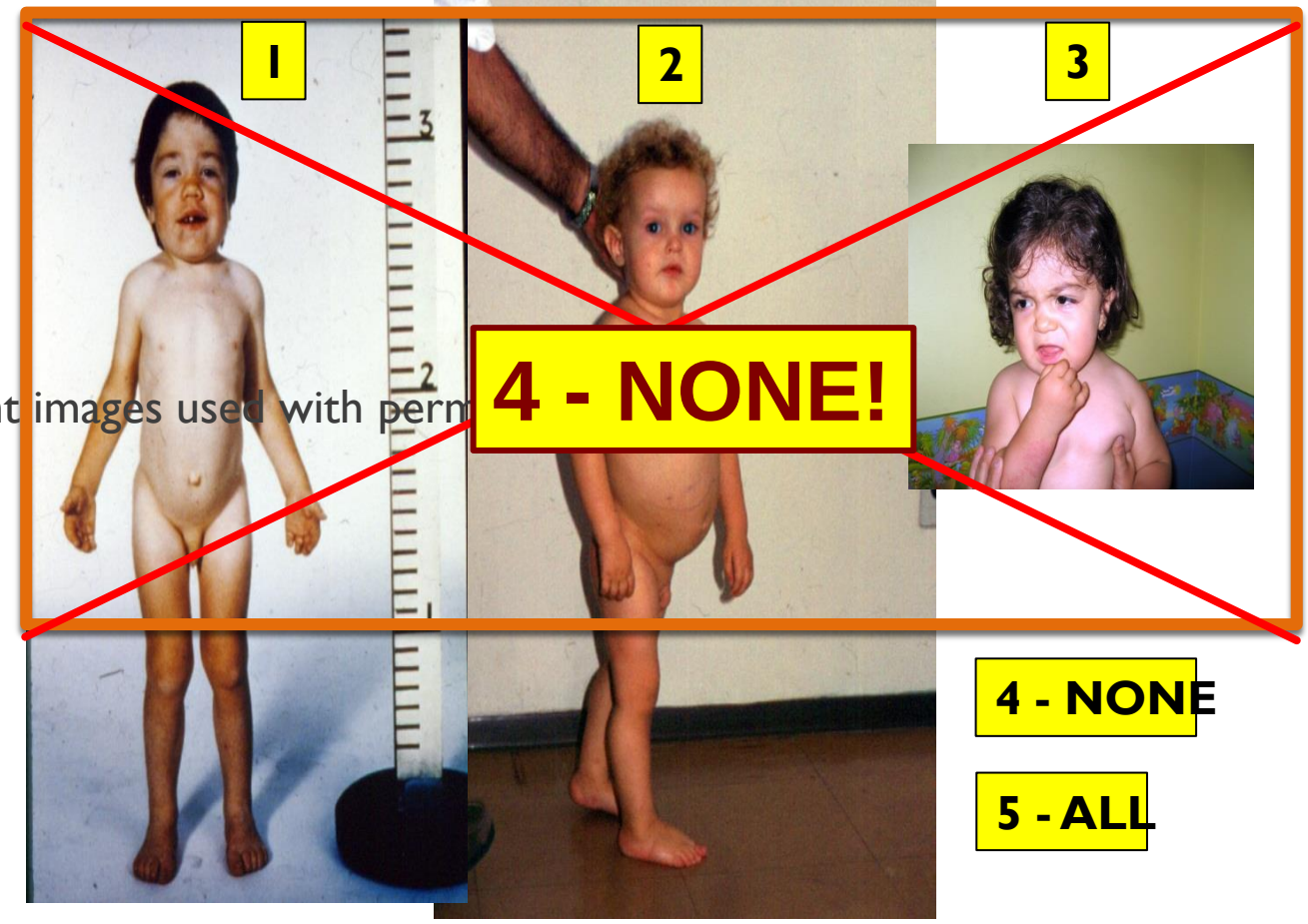
Beck et al., 2014

# WHEN SHOULD YOU CONSIDER MPS?

- Child born ‘normal’, slowly progressive course
- Coarse facies (not always)
- Corneal clouding (not always)
- Hepato- and/or splenomegaly (not always)
- Joint stiffness (not always)
- Bone dysplasia (may be mild)
- (Respiratory infections and/or distress)
- (Heart valve disease)
- (Previous surgery – mainly for hernia, tonsils)
- Cognitive decline (in some cases, may be prominent)

# QUIZ 1: WHICH OF THESE PATIENTS HAS MPS?

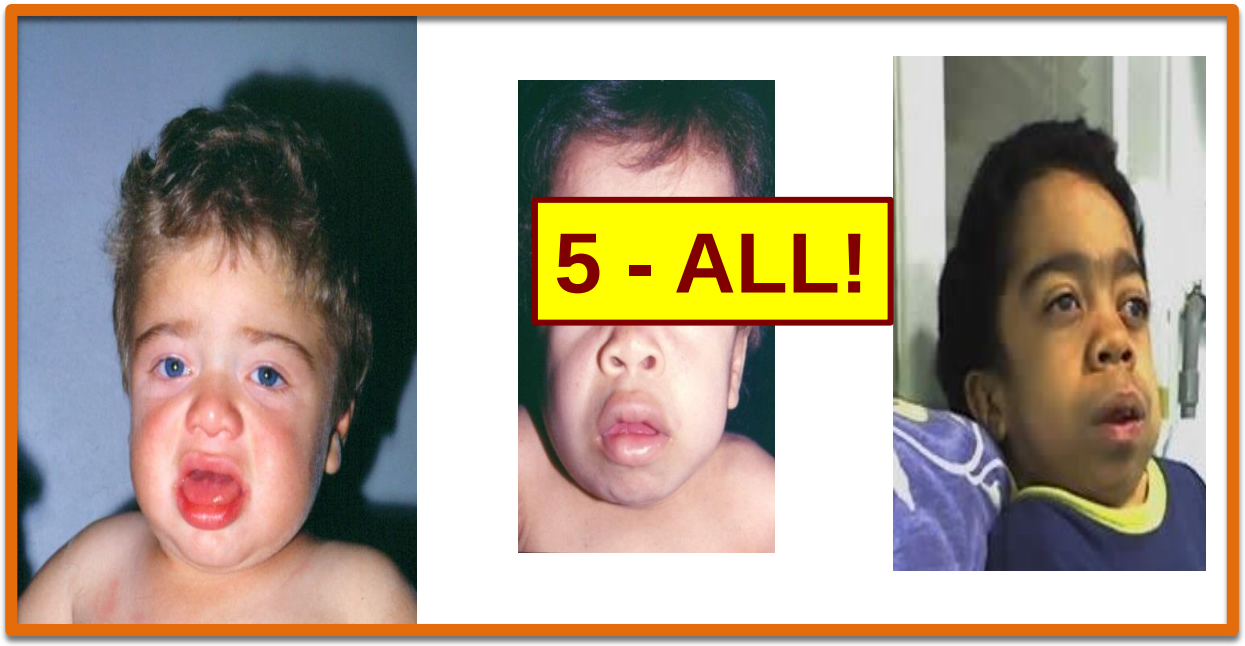
- Patient images used with perm



# QUIZ 2: WHICH OF THESE PATIENTS HAS MPS?

Patient images used with permission

1 2 3



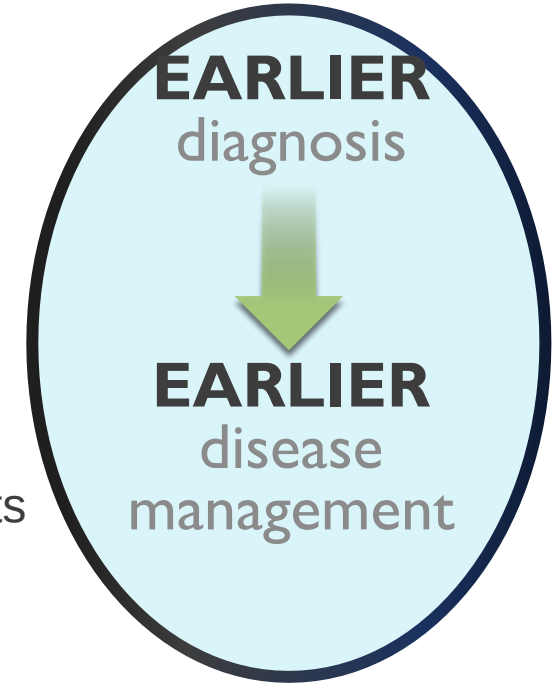

4 - NONE 5 - ALL

# 1ST-TAKE HOME MESSAGE

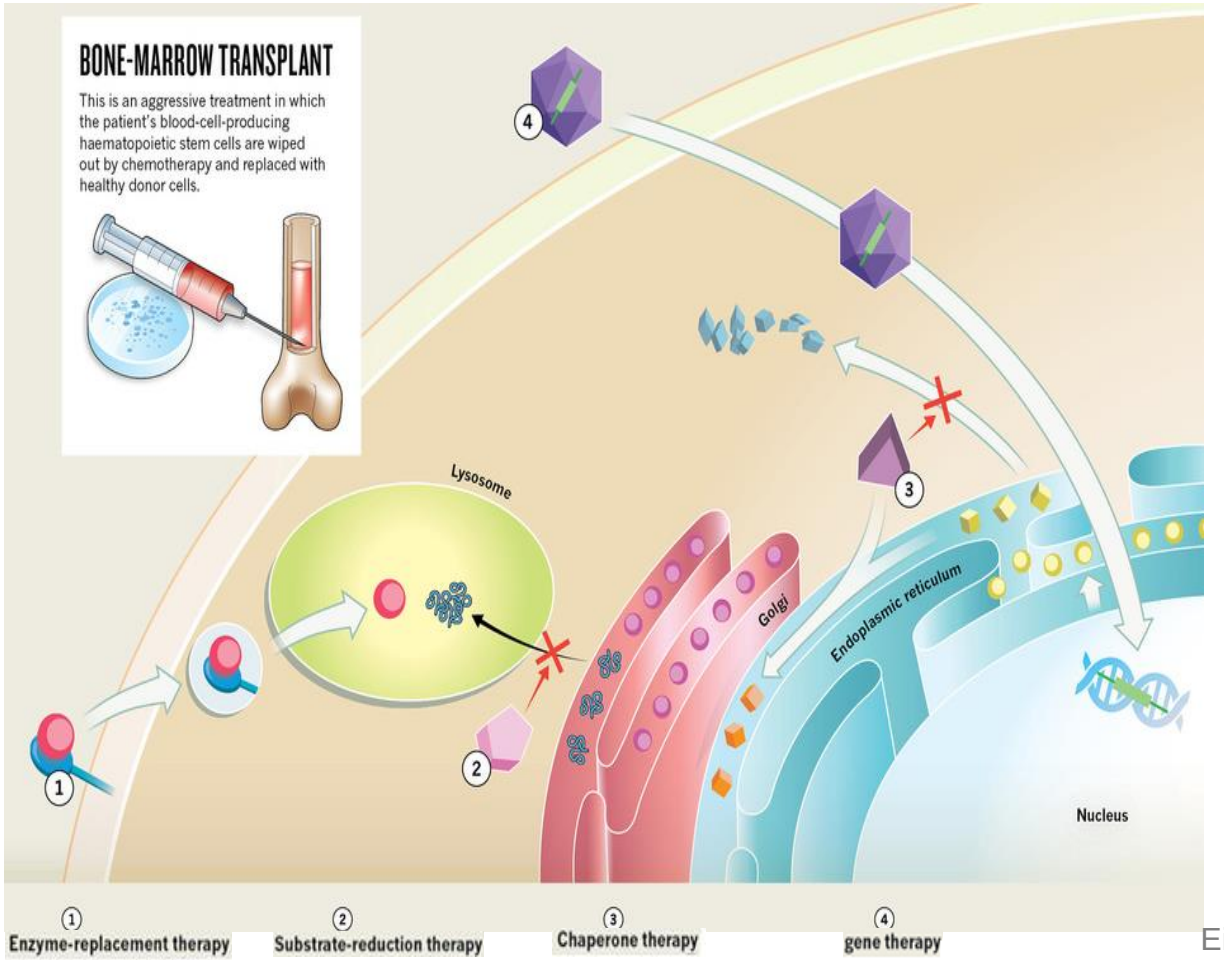
- Clinical suspicion is important, but you need the lab to make a diagnosis of MPS

# EARLY DIAGNOSIS IS KEY TO MANAGEMENT OF MPS

- Diagnosis may be based on a unique combination of symptoms rather than on a single presenting symptom
- Patients often visit multiple physicians before receiving a diagnosis of MPS
  - Diagnostic delays are common, particularly in patients with attenuated forms of MPS
- Screening of newborns in high-risk populations is not widespread, but may result in earlier diagnosis



# TREATMENTS




Eisenstein M, 2016

# TREATMENTS

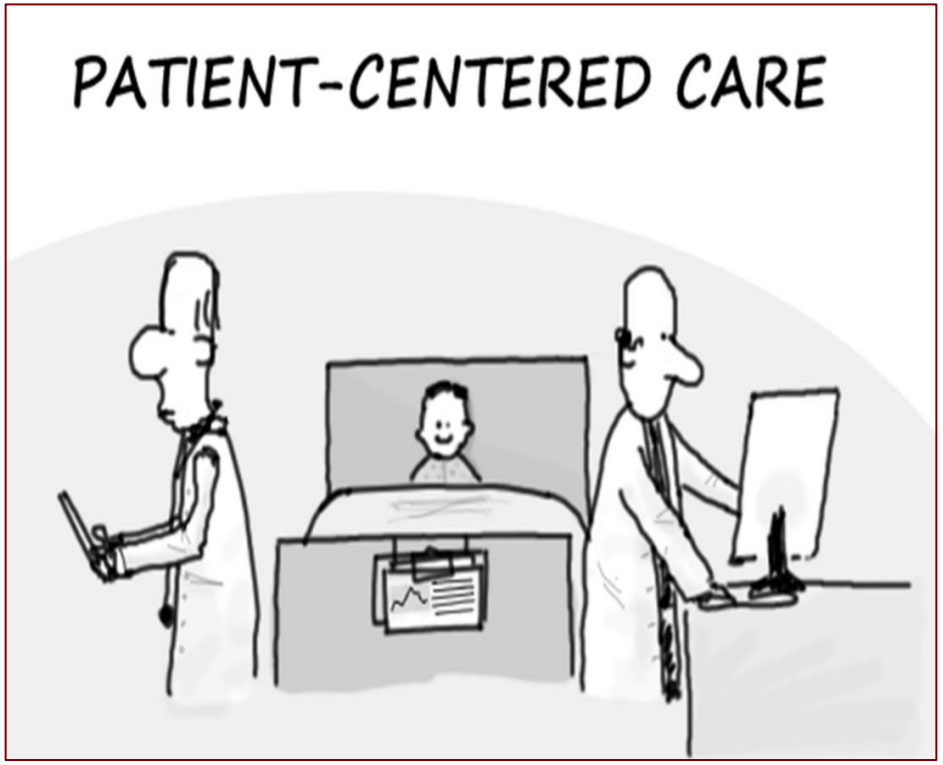
# TREATMENTS

# TREATMENTS

# TREATMENT- WHAT IS THE BEST?

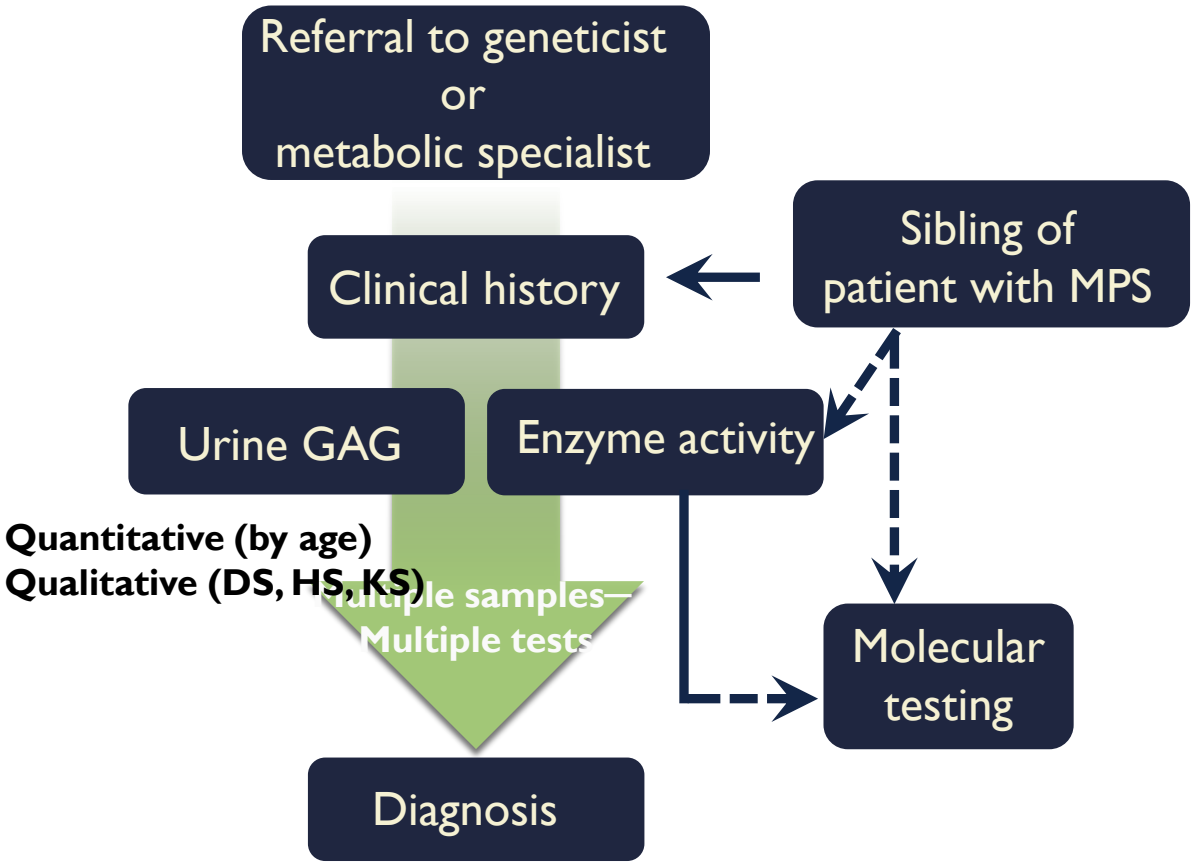
- ✓ Type of MPS
- ✓ Severity of the Phenotype
- ✓ Degree of System/Organ Involvement
  - (CNS, Bone, etc)
- ✓ Age of the Patient

# TREATMENT



# MULTIDISCIPLINARY TEAM

# DIAGNOSTIC ALGORITHM




DS, dermatan sulfate; HS, heparan sulfate; KS, keratan sulfate.
Lehman et al. 2011

# CURRENTLY AVAILABLE DIAGNOSTIC TESTS

- Urinary GAG test
  - Accumulation of GAGs in lysosomes results in elevated GAGs in the urine
  - May be qualitative or quantitative

- Enzyme assays
  - Measures activity of lysosomal enzymes
  - Required for definitive diagnosis
  - Commonly performed on dried blood spots

- Genetic testing
  - Identifies mutation(s)

# CLUSTERS IN LATIN AMERICA

- There is high allelic heterogeneity in all MPS genes, with high numbers of genetic mutations reported so far.

- MPS are considered ultra-rare disorders, but clusters of patients can be identified in some areas, usually associated to relative isolation, founder effect and endogamy.

- The aim of this work was to report clusters of MPS in Brazil, Dominican Republic, Ecuador, Haiti and Panama involving the types IIIB, IIIC, IVA and VI.

# SAMPLES AND METHODS

- Blood samples were obtained from 28 Ecuadorian patients, 43 Brazilian patients and 7 patients from Dominican Republic.

*Diagnoses*

- All patients were identified by low enzyme activity and confirmed by molecular analyses (Sanger sequencing [Applied 3500xL] and/or Next-generation sequencing [IonTorrent]).

*Bioinformatics analyses*

- To predict the possible pathogenicity of the novel variants detected, the Mutation Taster, SIFT and PredictSNP software were used.

# RESULTS

| Country | State | Number of patients | Type of MPS |
|---|---|---|---|
| Brazil | Paraíba (PB) | 7 | IIIC |
| Brazil | Paraíba (PB) | 23 | IVA |
| Brazil | Bahia (BA) | 13 | VI |
| Dominican Republic | Distrito Nacional | 7 | VI |
| Ecuador | Manabi | 20 | IIIB |
| Ecuador | Pastaza | 8 | IVA |

# RESULTS

Six clusters were identified in Brazil and Ecuador

**Figure 1:** Map of clusters in Ecuadorian (A), Brazil (B) and Dominican Republic (C)

# RESULTS

*Molecular analyses of MPS IIIB patients from Ecuador*

- Molecular analyses identified 17 homozygotes (85%) for the variant p.Leu496Pro, two compound heterozygotes (p.Leu496Pro/Arg482Gly; p.Leu496Pro/?) (10%). O estigation (Figure 2).

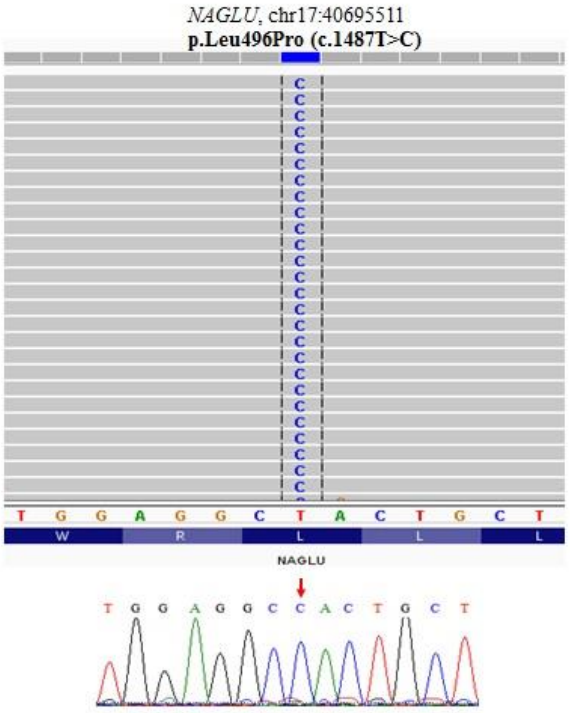



**Figure 2:** Next Generation se cing of *NAGLU* identifying p.Leu496Pro

# RESULTS

*Molecular analyses of MPS IIIC from Brazil*

- Molecular analyses identified the following variants: c.234+1G>A, c.372-2A>G, c.525dupT, p.Ser541Leu, c.1348delG, p.Asn258Ile (Martins et al. 2014).

*Molecular analyses of MPS IVA from Brazil*

- Molecular analyses identified 12 homozygotes (52%) and 3 heterozygotes for p.Ser341Arg (13%). All homozygote patients shared a common haplotype within the cluster. Haplotype analyses suggest a common ancestor (Bochernitsan et al., 2018).

*Molecular analyses of MPS IVA from Ecuador*

- Molecular analyses identified 8 homozygotes (100%) for p.Arg251Ter. This variant has been reported as disease associated (Morrone et al., 2014).

*Molecular analyses of MPS VI patients from Brazil*

- Molecular analyses identified 13 homozygotes (100%) for the variant p.His178Leu sharing the same haplotype within the cluster. Haplotype analyses suggest a common ancestor (Costa-Motta et al., 2014).

# RESULTS

*Molecular analyses of MPS VI patients from Dominican Republic*

- Molecular analyses identified 7 homozygotes (100%) for the variant p.His178Leu sharing the same haplotype within the cluster. Haplotype analyses suggest a common ancestor (Costa-Motta et al., 2014).

*Pathogenicity prediction*

- The variant identified in the MPS IIIB patients from Ecuador is classified with uncertain clinical significance by ClinVar. Polyphen prediction suggests that this alteration is probably damaging with conservation of this leucine in several species (Adzhubei et al., 2010).

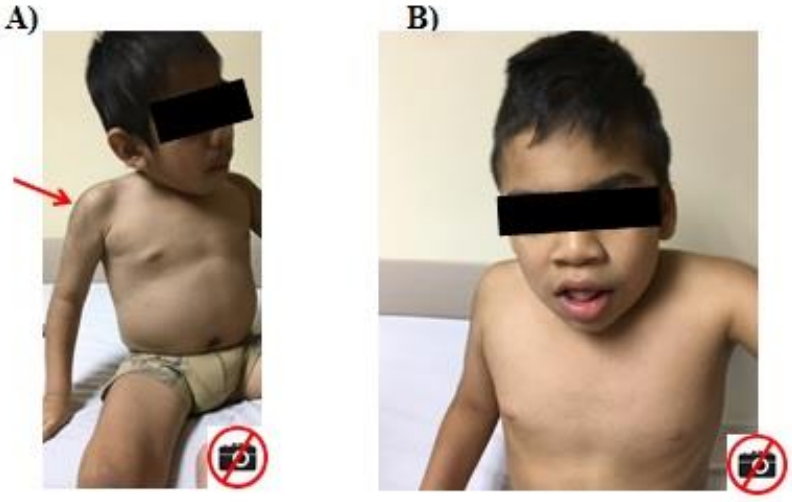
# RESULTS

- All MPS IIIB patients from Ecuador had a very severe phenotype suggesting that p.Leu496Pro in homozygosis could be associated with a severe phenotype (Figure 4).

**Figure 4:** Two untreated MPS type B patients homozygotes for p.Leu496Pro

a) 9 year old male; b) 10.1 year old male. Red arrow: note hypertricosis.

Consent obtained for image use.



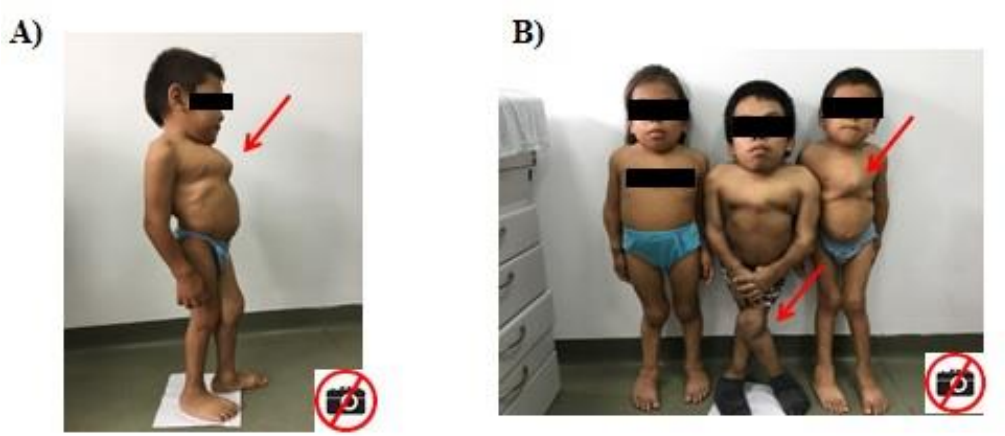
# RESULTS

- Likewise, all MPS IVA patients homozygotes for p.Arg251Ter had a very severe phenotype (Figure 5).

**Figure 5:** Three untreated siblings with MPS IVA homozygotes for p.Arg251Ter

a) 4.11 year old male; b) From left to right: 11.4 year old female, 21 year old male and 4.11 year old male. Red arrow: note *pectus carinatum*, genu valgum.

Consent obtained for image use.



# DISCUSSION AND CONCLUSIONS

- We report five MPS clusters in Brazil and Ecuador.
- Haplotype analyses were already performed in two clusters, suggesting a common ancestor.
- Our findings indicate that clusters of specific MPS types are not rare in Latin America, and provide an opportunity for targeted health care and community genetics actions, including specific management and general preventive measures.
- These findings are also important for epidemiological studies, genetic counseling and genotype-phenotype correlation.