

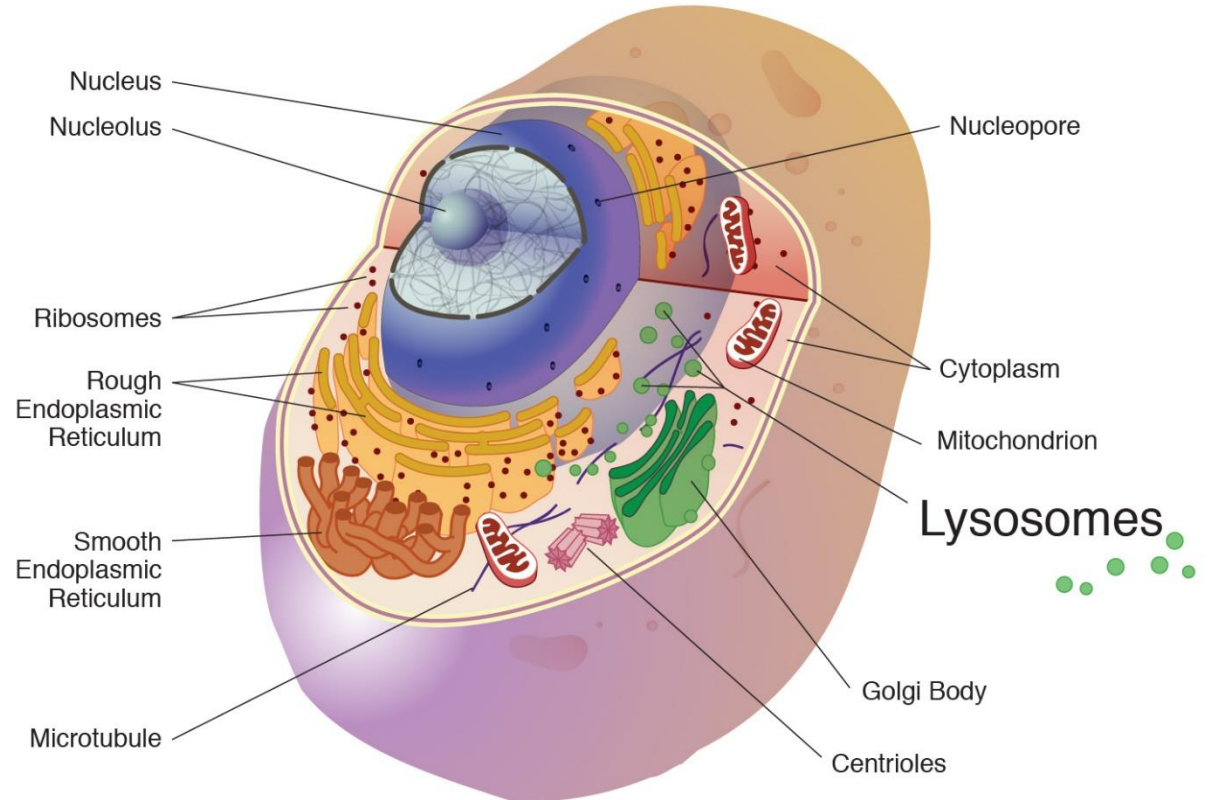
Lysosomal storage disorders

Manama training Clinical Genetics
Inborn errors of metabolism

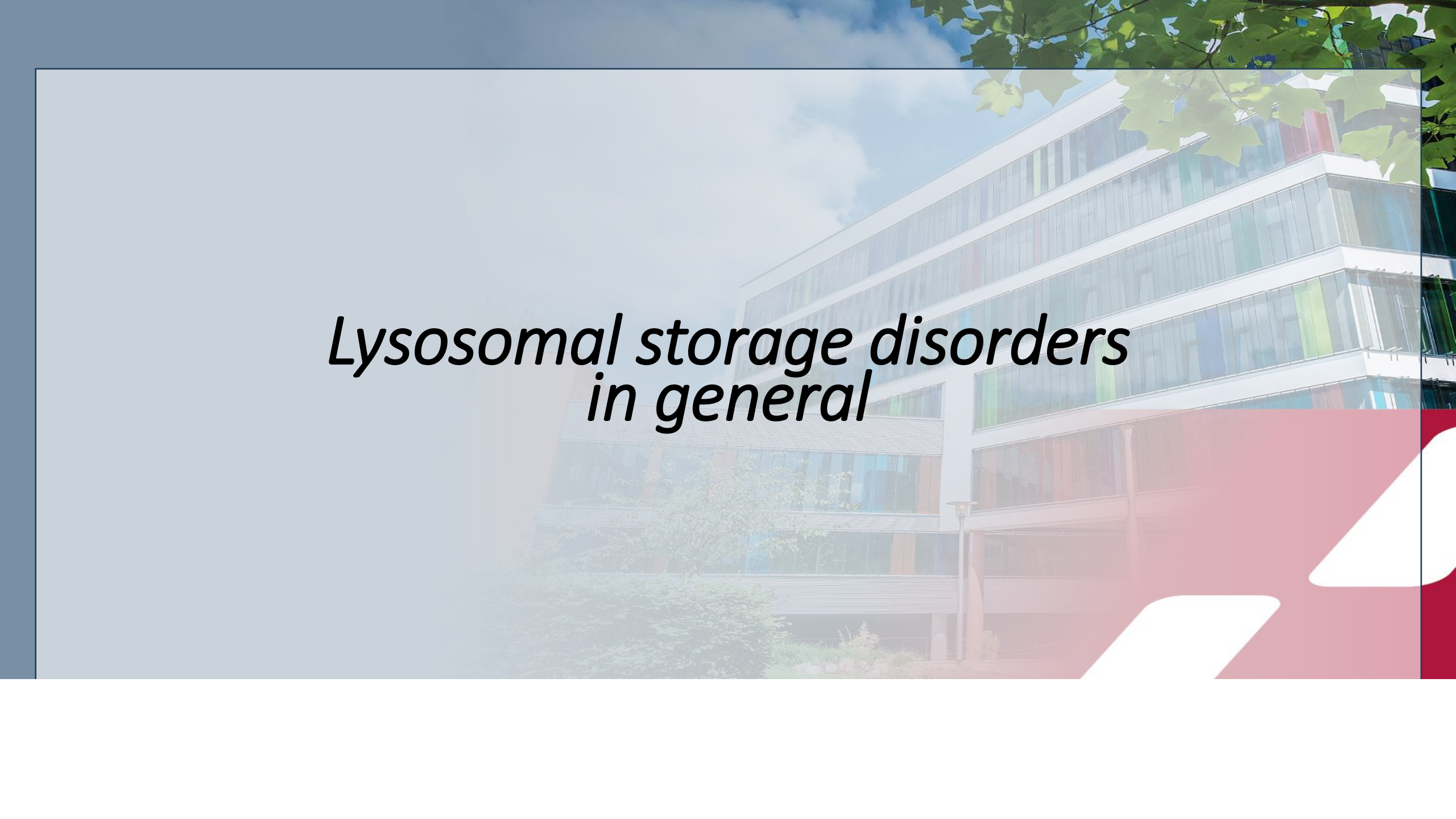
Sandra Kingma, MD PhD
Pediatrician Metabolic Disorders

Structure

- The lysosome
- Pathophysiology of lysosomal storage disorders
- Classification and inheritance
- Treatment
- LSDs:
 - MPSs
 - Pompe
 - Gaucher
 - Fabry



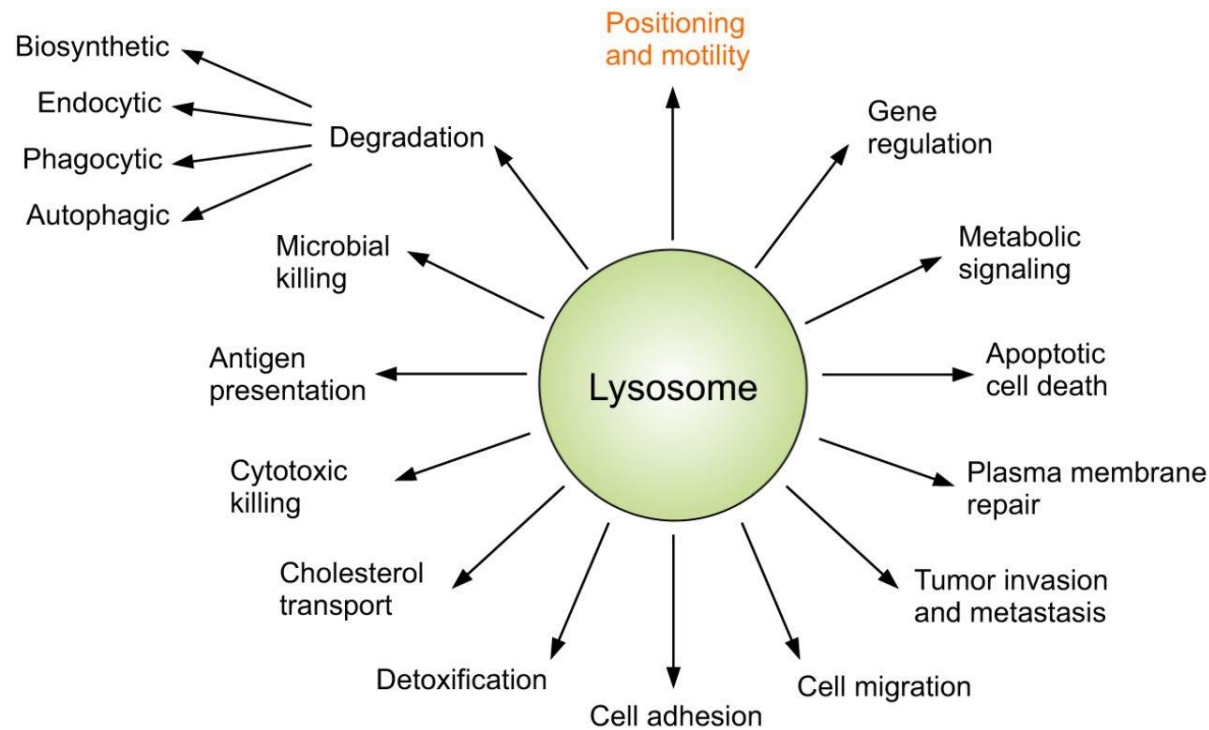
Ref: [https:// www.genome.gov/genetics-glossary/Lysosome](https://www.genome.gov/genetics-glossary/Lysosome)



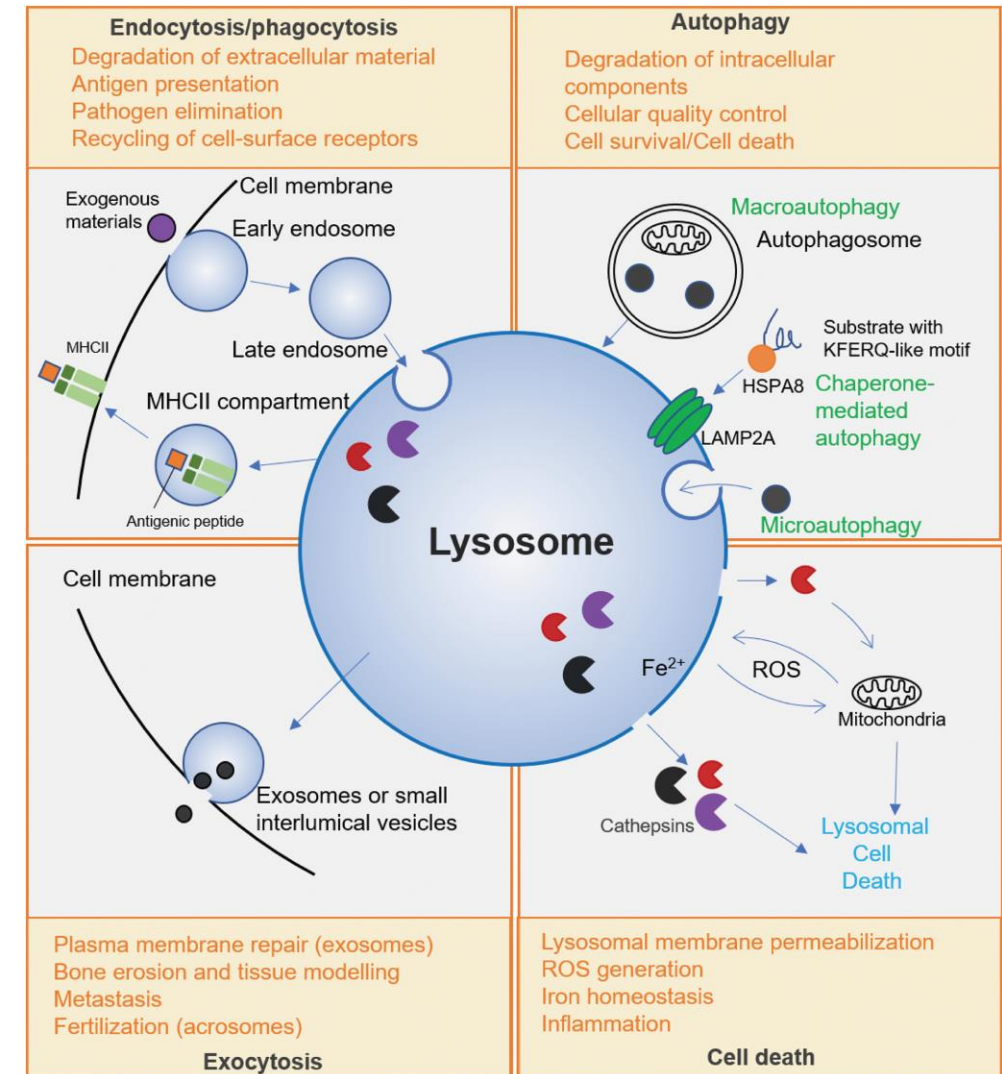
Lysosomal storage disorders in general

The lysosome

- Breakdown/recycling: autophagy, phagocytosis/breakdown macromolecules
- Metabolism/energy-balance
- Signal transduction (Ca)
- Development (cathepsins, etc), etc

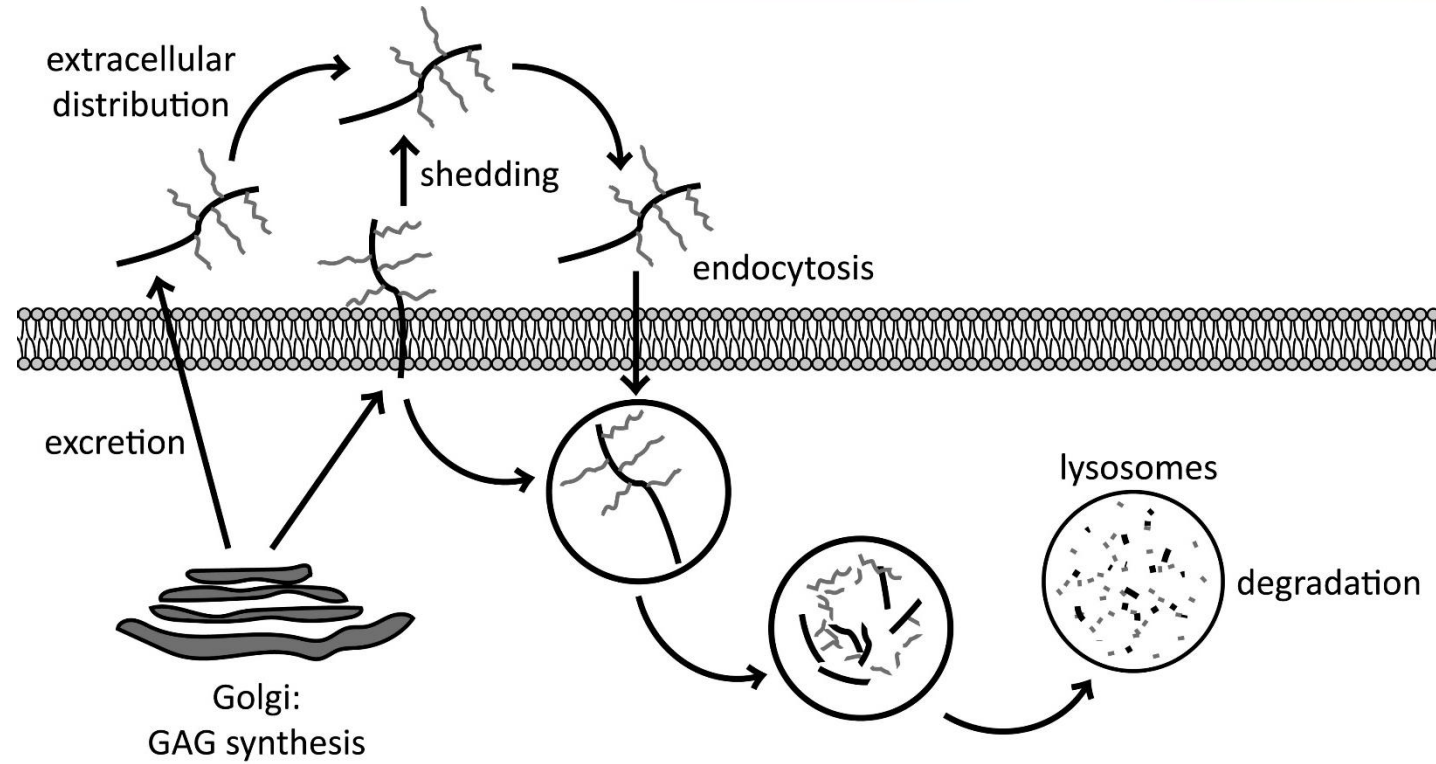
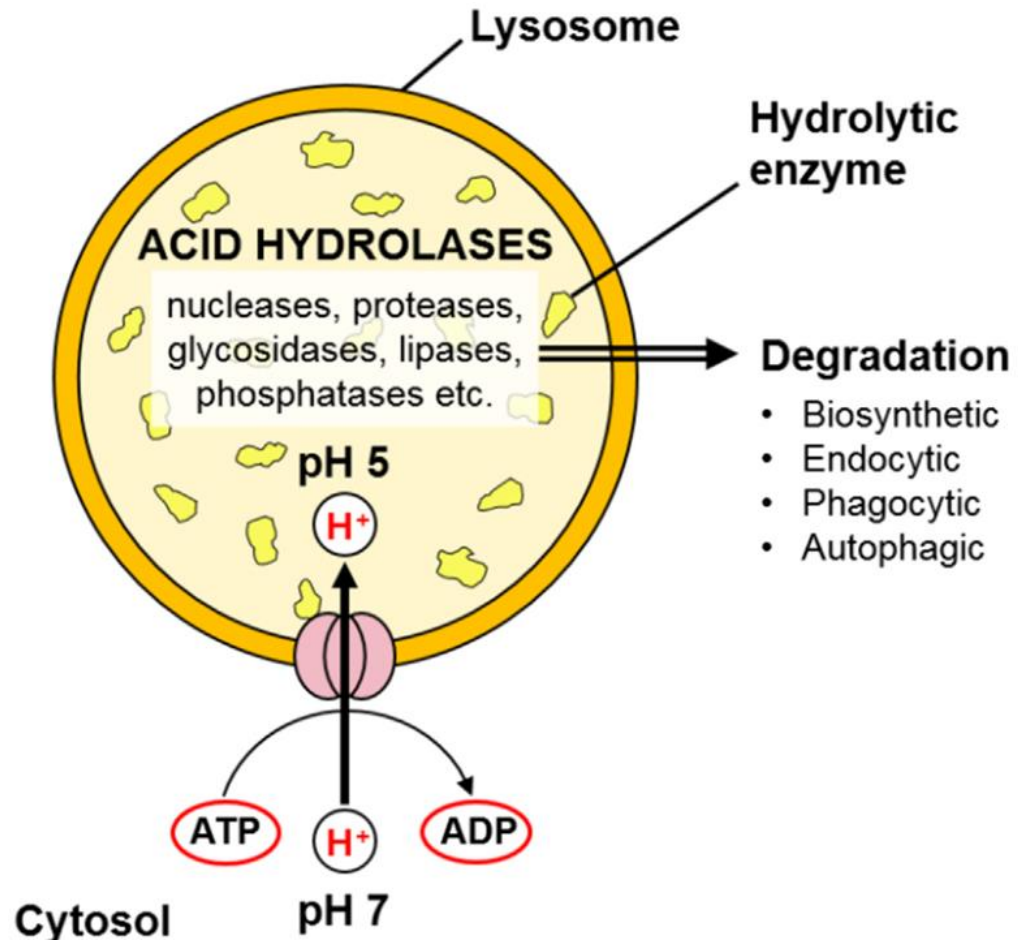


Settembre et al. Nat Rev Mol Cell Biol 2013 14:283-96



Wang et al. Traffic.
2018;19:918-931

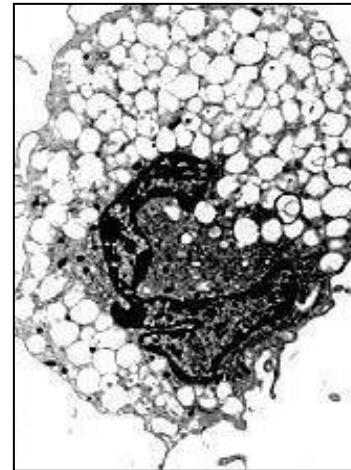
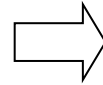
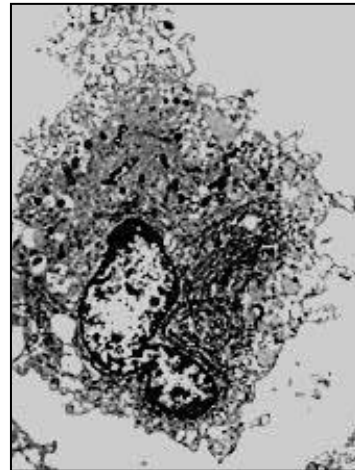
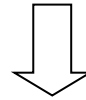
Degradation



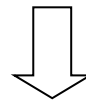
Kingma SDK (2015) PhD thesis: MPS I: pathophysiology, and therapy of bone disease.

Ref: Rathore et al. Biomaterials. 2019;211:25-47.

GAG degrading enzyme
deficiency



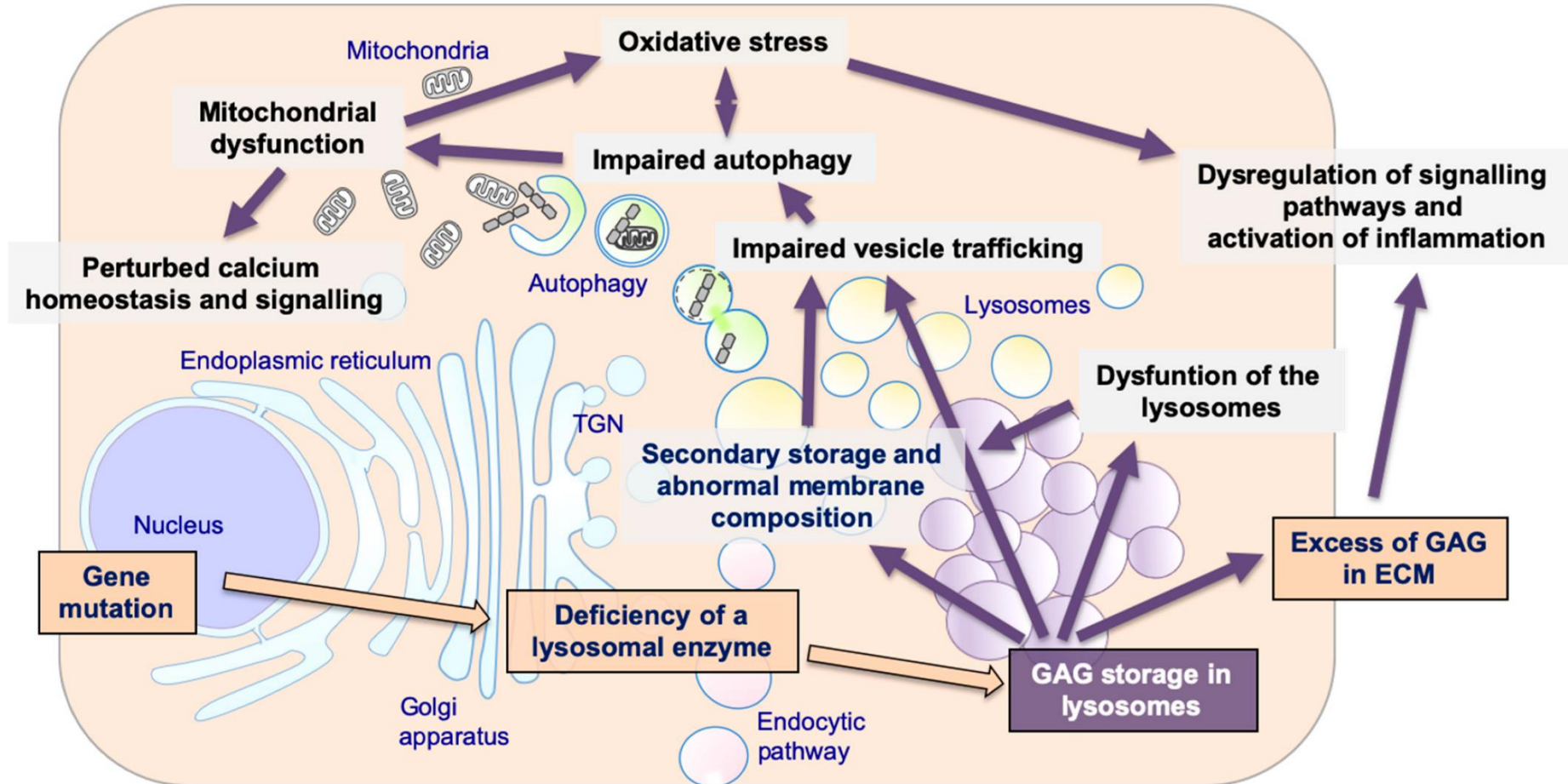
Modified from: Neufeld *et al.* The Metabolic and molecular
bases of inherited disease 2001



MPS phenotype; multiorgan dysfunction

Variants in genes that code
for lysosomal enzymes,
transporters or activator
proteins all can lead to
lysosomal storage disorders

Pathophysiology



Fecarotta et al. Pathogenesis of Mucopolysaccharidoses, an Update. *Int. J. Mol. Sci.* 2020, 21, 2515

Classification

<i>Sphingolipidoses</i>
• Fabry disease (<i>GLA</i>) • Farber lipogranulomatosis (<i>ASAH1</i>) • Gaucher disease (<i>GBA</i>) • GM1 gangliosidosis (<i>GLB1</i>) • GM2 gangliosidosis or Tay–Sachs disease (<i>HEXA</i>) • GM2 gangliosidosis or Sandhoff disease (<i>HEXB</i>) • GM2 gangliosidosis or GM2 activator deficiency (<i>GM2A</i>) • Krabbe disease (<i>GALC</i>) • Metachromatic leukodystrophy (<i>ARSA</i> and <i>PSAP</i>) • Niemann–Pick (A/B) (<i>SMPD1</i>)
<i>Lipid storage diseases</i>
• Acid lipase deficiency: Wolman disease and cholesterol ester storage disease (<i>LIPA</i>)

<i>Mucopolysaccharidoses</i>
• MPS I or Hurler Syndrome (<i>IDUA</i>) • MPS II or Hunter syndrome (<i>IDS</i>) • MPS IIIA (<i>SGSH</i>) • MPS IIIB (<i>NAGLU</i>) • MPS IIIC (<i>HGSNAT</i>) • MPS IIID (<i>GNS</i>) • MPS IVA (<i>GALNS</i>) • MPS IVB (<i>GLB1</i>) • MPS VI (<i>ARSB</i>) • MPS VII (<i>GUSB</i>) • MPS IX (<i>HYAL1</i>)
<i>Post- translational modification defects</i>
• Multiple sulfatase deficiency (<i>SUMF1</i>) • Mucopolipidosis II α/β, I-cell disease (<i>GNPTAB</i>) • Mucopolipidosis II α/β, pseudo-Hurler polydystrophy (<i>GNPTAB</i>) • Mucopolipidosis III γ, variant pseudo-Hurler polydystrophy (<i>GNPTG</i>)

<i>Glycoproteinoses</i>
• α- Mannosidosis (<i>MAN2B1</i>) • β- Mannosidosis (<i>MANBA</i>) • Fucosidosis (<i>FUCA1</i>) • Aspartylglucosaminuria (<i>AGA</i>) • Schindler disease (<i>NAGA</i>) • Sialidosis type I (<i>NEU1</i>) • Sialidosis type II (<i>NEU1</i>) • Galactosialidosis (<i>CTSA</i>)
<i>Integral membrane protein disorders</i>
• Cystinosis (<i>CTNS</i>) • Danon disease (<i>LAMP2</i>) • Action myoclonus-renal failure syndrome (<i>SCARB2</i>) • Sialic acid storage disease (<i>SLC17A5</i>) • Niemann–Pick disease types C1 and C2 (<i>NPC1</i> and <i>NPC2</i>) • Mucopolipidosis IV (<i>MCOLN1</i>)

<i>LRO disorders</i>
• Hermansky–Pudlak disease type 1 (<i>HPS1</i>) • <i>HPS2</i> (<i>AP3B1</i>) • <i>HPS3</i> • <i>HPS4</i> • <i>HPS5</i> • <i>HPS6</i> • <i>HPS7</i> • <i>HPS8</i> (<i>BLOC1S3</i>) • <i>HPS9</i> • Griscelli syndrome 1 (<i>MYO5A</i>) • Griscelli syndrome 2 (<i>RAB27A</i>) • Chédiak–Higashi disease (<i>LYST</i>)
<i>Glycogen storage disease</i>
• Pompe disease (<i>GAA</i>)

<i>Neuronal ceroid lipofuscinoses</i>
• CLN1 (<i>PPT1</i>) • CLN2 (<i>TPP1</i>) • CLN3 (<i>CLN3</i>) • CLN4 (<i>DNAJC5</i>) • CLN5 (<i>CLN5</i>) • CLN6 (<i>CLN6</i>) • CLN7 (<i>MFSD8</i>) • CLN8 (<i>CLN8</i>) • CLN9 (N/A) • CLN10 (<i>CTSD</i>) • CLN11 (<i>GRN</i>) • CLN12 (<i>ATP13A2</i>) • CLN13 (<i>CTSF</i>) • CLN14 (<i>KCTD7</i>)

La Cognata et al. Highlights on Genomics Applications for Lysosomal Storage Diseases. Cells 2020, 9, 1902.

Mode of inheritance

Sphingolipidoses - Fabry disease (<i>GLA</i>) - Farber lipogranulomatosis (<i>ASAHI</i>) - Gaucher disease (<i>GBA</i>) - GM1 gangliosidosis (<i>GLB1</i>) - GM2 gangliosidosis or Tay–Sachs disease (<i>HEXA</i>) - GM2 gangliosidosis or Sandhoff disease (<i>HEXB</i>) - GM2 gangliosidosis or GM2 activator deficiency (<i>GM2A</i>) - Krabbe disease (<i>GALC</i>) - Metachromatic leukodystrophy (<i>ARSA</i> and <i>PSAP</i>) - Niemann–Pick (A/B) (<i>SMPD1</i>)	Mucopolysaccharidoses - MPS I or Hurler Syndrome (<i>IDUA</i>) - MPS II or Hunter syndrome (<i>IDS</i>) - MPS IIIA (<i>SGSH</i>) - MPS IIIB (<i>NAGLU</i>) - MPS IIIC (<i>HGSNAT</i>) - MPS IIID (<i>GNS</i>) - MPS IVA (<i>GALNS</i>) - MPS IVB (<i>GLB1</i>) - MPS VI (<i>ARSB</i>) - MPS VII (<i>GUSB</i>) - MPS IX (<i>HYAL1</i>)	Glycoproteinoses - α- Mannosidosis (<i>MAN2B1</i>) - β- Mannosidosis (<i>MANBA</i>) - Fucosidosis (<i>FUCA1</i>) - Aspartylglucosaminuria (<i>AGA</i>) - Schindler disease (<i>NAGA</i>) - Sialidosis type I (<i>NEU1</i>) - Sialidosis type II (<i>NEU1</i>) - Galactosialidosis (<i>CTSA</i>)	LRO disorders - Hermansky–Pudlak disease type 1 (<i>HPS1</i>) <i>HPS2</i> (<i>AP3B1</i>) <i>HPS3</i> <i>HPS4</i> <i>HPS5</i> <i>HPS6</i> <i>HPS7</i> <i>HPS8</i> (<i>BLOC1S3</i>) <i>HPS9</i> - Griselli syndrome 1 (<i>MYO5A</i>) - Griselli syndrome 2 (<i>RAB27A</i>) - Chédiak–Higashi disease (<i>LYST</i>)	Neuronal ceroid lipofuscinoses - CLN1 (<i>PPT1</i>) - CLN2 (<i>TPP1</i>) - CLN3 (<i>CLN3</i>) - CLN4 (<i>DNAJC5</i>) - CLN5 (<i>CLN5</i>) - CLN6 (<i>CLN6</i>) - CLN7 (<i>MFSD8</i>) - CLN8 (<i>CLN8</i>) - CLN9 (N/A) - CLN10 (<i>CTSD</i>) - CLN11 (<i>GRN</i>) - CLN12 (<i>ATP13A2</i>) - CLN13 (<i>CTSF</i>) - CLN14 (<i>KCTD7</i>)
Lipid storage diseases Acid lipase deficiency: Wolman disease and cholesterol ester storage disease (<i>LIPA</i>)	Post- translational modification defects - Multiple sulfatase deficiency (<i>SUMF1</i>) - Mucopolipidosis II α/β, I-cell disease (<i>GNPTAB</i>) - Mucopolipidosis II α/β, pseudo-Hurler polydystrophy (<i>GNPTAB</i>) - Mucopolipidosis III γ, variant pseudo-Hurler polydystrophy (<i>GNPTG</i>)	Integral membrane protein disorders - Cystinosis (<i>CTNS</i>) - Danon disease (<i>LAMP2</i>) - Action myoclonus–renal failure syndrome (<i>SCARB2</i>) - Sialic acid storage disease (<i>SLC17A5</i>) - Niemann–Pick disease types C1 and C2 (<i>NPC1</i> and <i>NPC2</i>) - Mucopolipidosis IV (<i>MCOLN1</i>)	Glycogen storage disease Pompe disease (<i>GAA</i>)	

La Cognata et al. Highlights on Genomics
Applications for Lysosomal Storage
Diseases. Cells 2020, 9, 1902.

Mostly autosomal
recessive

X-linked:

- MPS II (*IDS*)
- Fabry (*GLA*)
- Danon (*LAMP2*)

Autosomal dominant:

- CLN4 (*DNAJC5*)

Current therapies

Enzyme replacement therapy

- Gaucher 1/3
- Fabry
- Pompe
- MPS I, II, IVA, VI, VII
- Niemann–Pick B (ASMD)
- CLN2 (intrathecal ERT)

Hematopoietic stem cell transplantation

- MPS I (severe)
- Krabbe (presymptomatic)
- Chediak–Higashi
- Griscelli type II

Several emerging or experimental therapies

Substrate reduction therapy

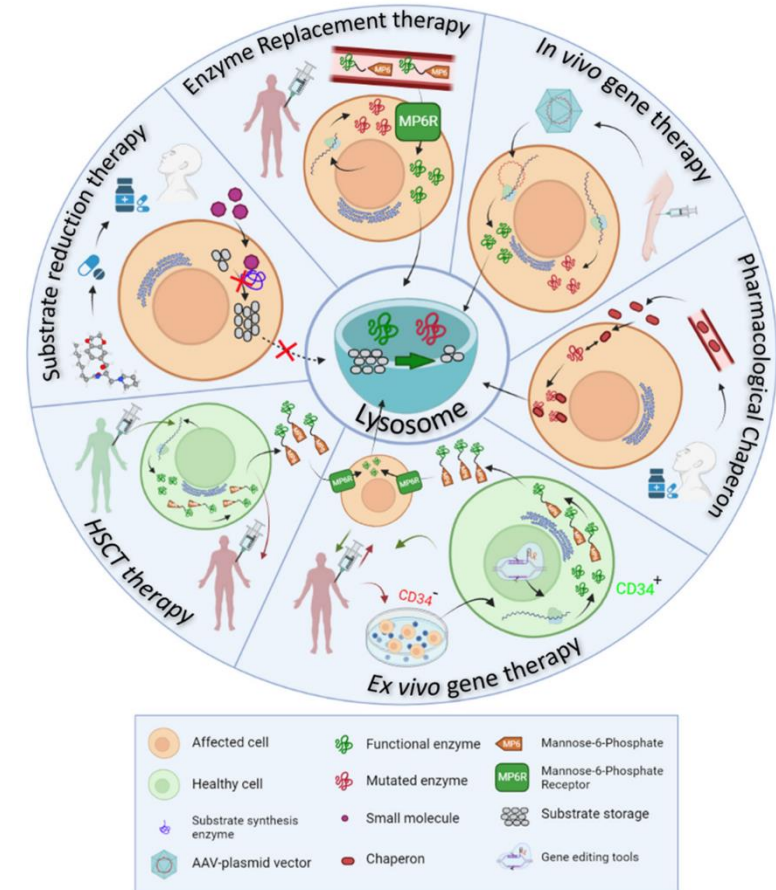
- Gaucher 1: eliglustat, miglustat
- Niemann–Pick C: miglustat

Gene therapy

- MLD: Libmeldy

Chaperone therapy

- Fabry: migalastat



Fernández-Pereira, C et al. Therapeutic Approaches in Lysosomal Storage Diseases. *Biomolecules* **2021**, 11, 1775.

Current therapies – disorders to discuss

Enzyme replacement therapy

- Gaucher 1/3 ←
- Fabry ←
- Pompe ←
- MPS I, II, IVA, VI, VII ←
- Niemann–Pick B (ASMD)
- CLN2 (intrathecal ERT)



Substrate reduction therapy

- Gaucher 1: eliglustat, miglustat
- Niemann–Pick C: miglustat

Gene therapy

- MLD: Libmeldy

Hematopoietic stem cell transplantation

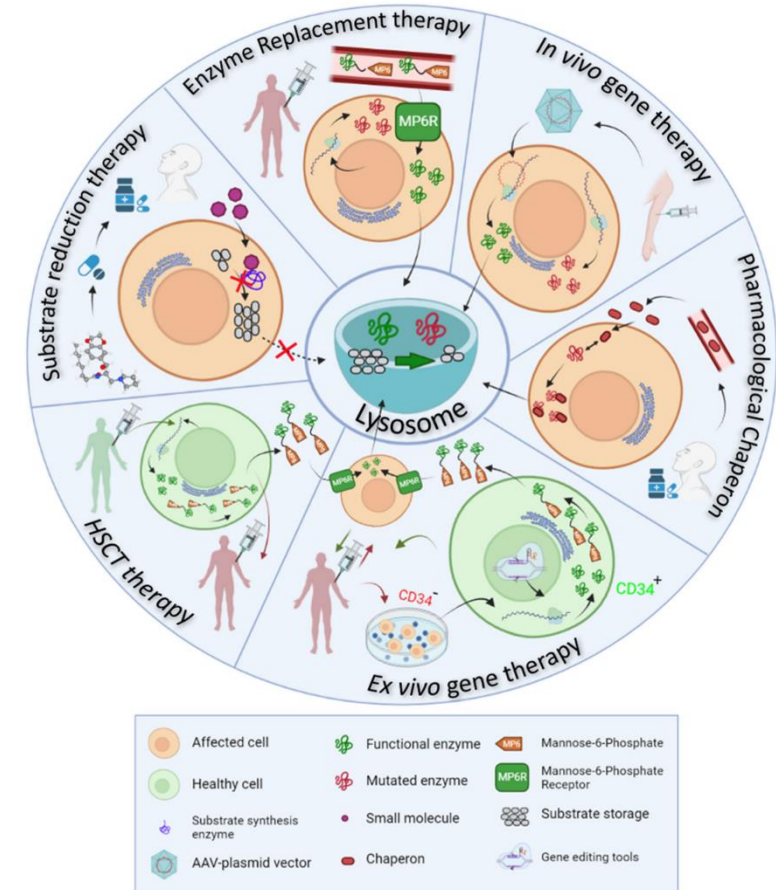
- MPS I (severe) ←
- Krabbe (presymptomatic)
- Chediak–Higashi
- Griscelli type II



Chaperone therapy

- Fabry: migalastat

Several emerging or experimental therapies

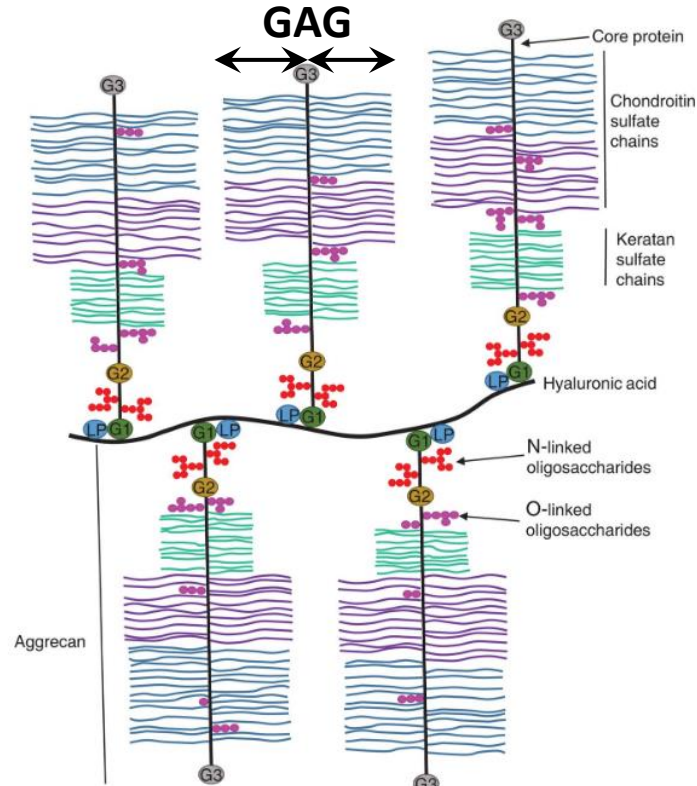


Fernández-Pereira, C et al. Therapeutic Approaches in Lysosomal Storage Diseases. *Biomolecules* **2021**, 11, 1775.

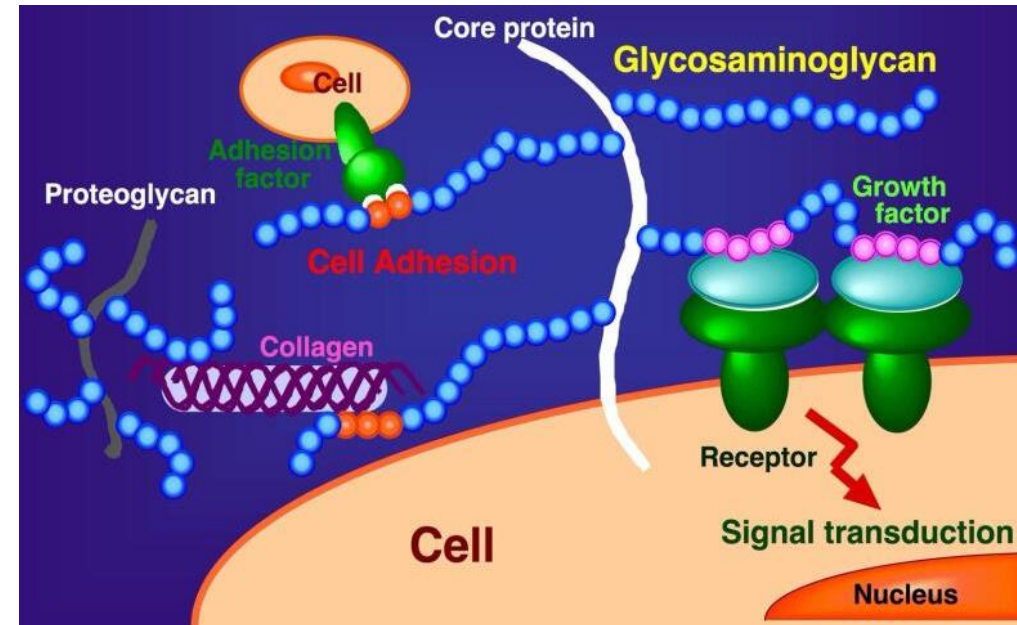


The mucopolysaccharidoses

The mucopolysaccharidoses

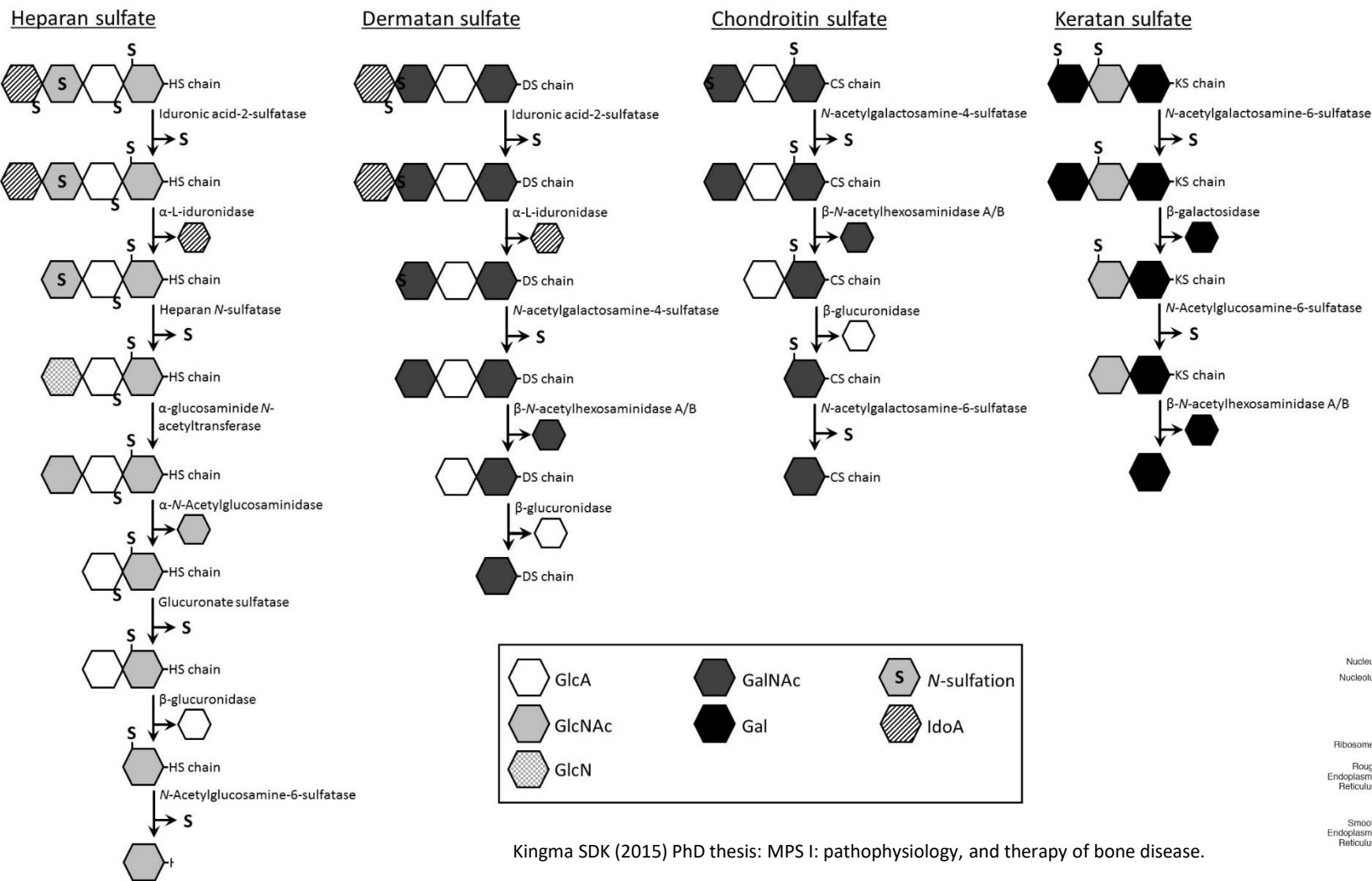


Baynes, John W., Dominiczak, Marek H. (2022). *Medical Biochemistry*, 6th ed.: Elsevier.

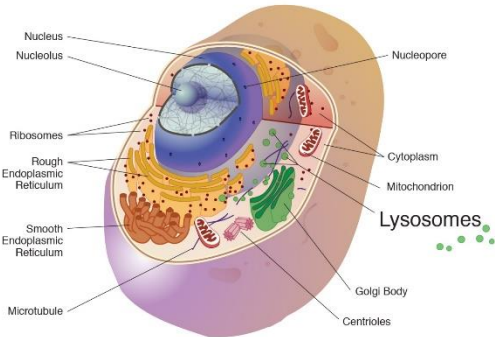


Mizumoto S, Yamada S. Preparation of glycosaminoglycans. 2021 Oct 6 [Updated 2022 Mar 30]. In: Nishihara S, Angata K, Aoki-Kinoshita KF, et al., editors. *Glycoscience Protocols (GlycoPODv2)* [Internet]. Saitama (JP): Japan Consortium for Glycobiology and Glycotechnology; 2021-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK593958/>

The mucopolysaccharidoses

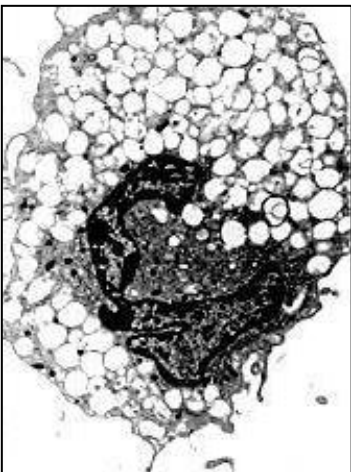
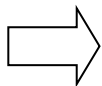
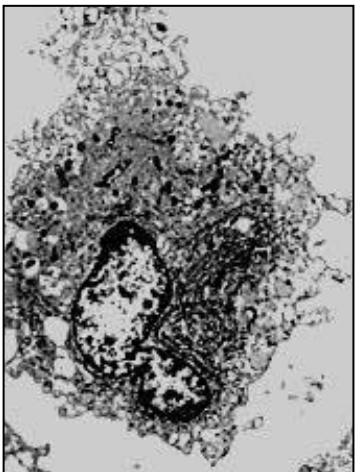
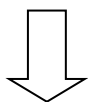


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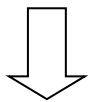


The mucopolysaccharidoses

GAG degrading
enzyme deficiency



Modified from: Neufeld *et al.* The Metabolic and molecular bases of inherited disease 2001



MPS phenotype; multiorgan dysfunction

MPS	Associated Gene	Deficient Enzyme	GAG Accumulation
MPS I	<i>IDUA</i>	α -L-iduronidase	HS, DS
MPS II	<i>IDS</i>	iduronidase-2-sulfatase	HS, DS
MPS IIIA	<i>SGSH</i>	heparan-N-sulfatase	HS
MPS IIIB	<i>NAGLU</i>	α -N-acetylglucosaminidase	HS
MPS IIIC	<i>HGSNAT</i>	α -glucosaminidase acetyltransferase	HS
MPS IIID	<i>GNS</i>	N-acetylglucosamine-6-sulfatase	HS
MPS IVA	<i>GALNS</i>	N-acetylglucosamine-6-sulfate sulfatase	KS, DS
MPS IVB	<i>GLB1</i>	β -galactosidase	KS
MPS VI	<i>ARSB</i>	N-acetylglucosamine-4-sulfatase	DS
MPS VII	<i>GUSB</i>	β -glucuronidase	HS, DS, CS
MPS IX	<i>HYAL1</i>	Hyaluronidase	Hyaluronan
MPS X	<i>ARSK</i>	Arylsulfatase K	DS
MPS plus	<i>VPS33A</i>		HS, DS
MPS like	<i>VPS16</i>		

The mucopolysaccharidoses

Cumulative incidence: 1:4.000
- 1:13.000

Kingma SD et al. Epidemiology and diagnosis of lysosomal storage disorders; challenges of screening. Best Pract Res Clin Endocrinol Metab. 2015 Mar;29(2):145-57.

Multisystem, chronic diseases.
2/3 of LSDs associated with neurological involvement.
Despite substantial progress, approved therapies for LSDs have important limitations

Pathophysiology still poorly understood.



Developmental delay, regression

Ocular manifestations

Hearing loss

Facial dysmorphisms

Upper respiratory tract obstruction/infection

Recurrent lung infections

Cardiac involvement, valve disease

Visceromegaly, hernias

Gastro-intestinal manifestations

Joint stiffness, skeletal dysmorphisms

MPS phenotypes



From: Neufeld *et al.* Scriver's OMMBID 1995



From: Horovitz *et al.* MGM Rep 2015



From: Parini *et al.* Acta Paediatrica 2018



Burton *et al.* Eur J Ped 2012



Hendriksz *et al.* AJMG 2014



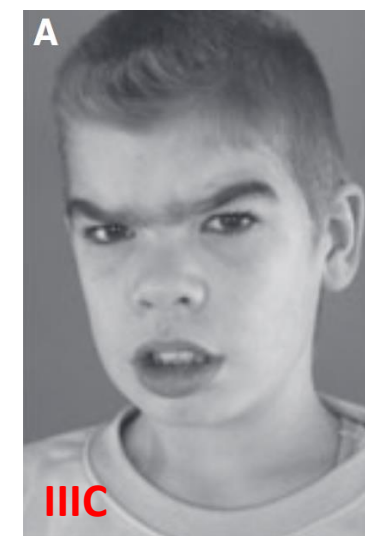
Sly *et al.* J. Ped 1973



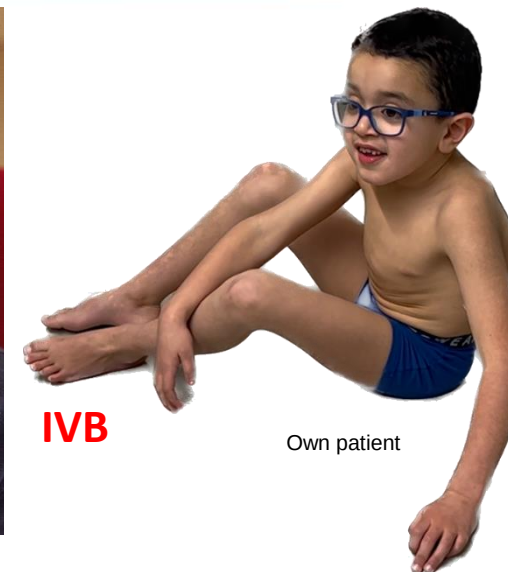
Own patient



Valayannopoulos *et al.* OJRD 2010



From: Wijburg *et al.* Acta Paediatr 2013



Own patient



From: Parini *et al.* Acta Paediatrica 2018



Table 2

Differential diagnosis of LSDs for specific clinical signs or symptoms frequently observed in these disorders.

Presenting feature	Disease
Neurologic	
Carpal tunnel syndrome	ML II/III, MPS I/II/VI
Cerebellar ataxia	GM1/2 gangliosidosis, NPC, Krabbe, NCLs
Deafness	Fabry, Krabbe, α/β -mannosidosis, ML II/III, MPS I/II/IV, MSD
Hydrocephalus	Gaucher, α -mannosidosis, MPS I/VII, MSD, NPC, sialidosis
Hypotonia (Neonatal/early infancy)	Aspartylglucosaminuria, Danon, GM1 gangliosidosis, NPA/B, NPC, galactosialidosis, Krabbe, ML II/III, NPC, Pompe, sialidosis
Neuropathic pain	Fabry, MLD
Seizures (Predominantly present)	Krabbe, ML II/III, NCL, Schindler, GM2 gangliosidosis
Vision loss	Krabbe, ML IV, MLD, MSD, NCLs, Schindler, sialidosis
White matter abnormalities	Fucosidosis, Krabbe, MLD, SASD
Cardiovascular	
Cardiomyopathy	Aspartylglucosaminuria, Danon, Fabry, Gaucher, GM1 gangliosidosis, ML II/III, MPS I/II/IV/VI, Pompe, SASD, sialidosis
Valvular heart disease	Fabry, galactosialidosis, ML II/III, MPS I/II/IV/VI
Ocular	
Cherry red spot	NPA/B, Farber, galactosialidosis, GM1/2 gangliosidosis, sialidosis
Corneal clouding	galactosialidosis, GM1 gangliosidosis, ML II/III, ML IV, MPS I/II/IV/VI/VII, sialidosis
Saccadic eye movement disorder	Gaucher, NPC
Glaucoma	ML II/III, MPS I/VI
Other	
Neonatal jaundice	LAL deficiency, NPA/B, NPC
Hydrops foetalis	Farber, galactosialidosis, Gaucher, GM1 gangliosidosis, LAL deficiency, ML II/III, MPS IV/VII, NPA/B, NPC, SASD, sialidosis
Isolated organomegaly	Gaucher disease, LAL deficiency, NPA/B
Kidney failure	Cystinosis, Fabry

LAL lysosomal acid lipase, ML mucopolipidosis, MLD metachromatic leukodystrophy, MPS Mucopolysaccharidosis, MSD multiple sulfatase deficiency, NCL neuronal ceroid lipofuscinosis, NPA/B Niemann Pick type A/B, NPC Niemann Pick type C, SASD sialic acid storage disease.

The MPSs: Disease modifying therapies

MPS	Treatment
MPS I	- Severe and early diagnosis: HSCT - Attenuated: ERT (Aldurazyme)
MPS II	- ERT (Elaprase) - HSCT may be considered
MPS III	Supportive
MPS IVA	ERT (Elosulfase alfa) – longterm outcome?
MPS IVB	Supportive
MPS VI	- ERT (Naglazyme) - (HSCT may be considered)
MPS VII	- ERT (vestronidase alfa) - (HSCT may be considered, results variable)
MPS IX	Supportive
MPS X	Supportive
MPS plus	Supportive
MPS like	Supportive

Evolving therapies:

- Targeted ERT
- Anti-inflammatory
- Gene therapy
- Genome editing

The MPSs: Disease modifying therapies

MPS	Treatment
MPS I	- Severe en early diagnosis: HSCT - Attenuated: ERT (Aldurazyme)
MPS II	- ERT (Elaprase) - HSCT may be considered
MPS III	Supportive
MPS IVA	ERT (Elosulfase alfa) – limited effect
MPS IVB	Supportive
MPS VI	- ERT (Naglazyme) - (HSCT may be considered)
MPS VII	- ERT (vestronidase alfa) - (HSCT may be considered, results variable)
MPS IX	Supportive
MPS X	Supportive
MPS plus	Supportive
MPS like	Supportive

- Treatment as early as possible
- Before irreversible disease manifestations
- ERT does not cross BBB
- HSCT cannot restore cognitive function

MPS I

- HSCT before age 2 years
- Transplantation <9 months is optimal for long-term cognitive outcomes

	Australia	The Netherlands	British Columbia	Portugal	Czech Republic	United Arab Emirates
	1999	1999	2000	2004	2010	2013
	[7]	[8]	[3]	[10]	[6]	[4]
Mucopolysaccharidoses						
Mucopolysaccharidosis type I	1.14	1.19	0.58	1.33	0.72	0.25
Mucopolysaccharidosis type II	0.74	0.65	0.10	1.09	0.43	0
Mucopolysaccharidosis type IIIA	0.88	1.16	0.29	0	0.47	0
Mucopolysaccharidosis type IIIB	0.47	0.42		0.72	0.02	1.05
Mucopolysaccharidosis type IIIC	0.07	0.21		0.12	0.42	
Mucopolysaccharidosis type IIID	0.09	0.10			0	0
Mucopolysaccharidosis type IVA	0.59	0.22	0.48	0.6	0.71	1.41
Mucopolysaccharidosis type IVB		0.14			0.02	
Mucopolysaccharidosis type VI	0.43	0.15	0.48	0.42	0.05	2.51
Mucopolysaccharidosis type VII	0.05	0.24	0.29	0	0.02	

Birth prevalences of LSDs reported in different countries, expressed as cases per 100,000 live births.

Modified from: Kingma *et al.* Best Prac Res Clin Endocrinol Metab 2015.

Difference in age, onset and phenotype



Own patient. Age: 9 months

TABLE 2 Clinical manifestations with an onset before the age of 1 and 6 months

Early onset symptoms <1 month old	Early onset symptoms <6 months old
Upper respiratory tract obstruction	Coarse facial features
Inguinal hernia	Inguinal hernia
Congenital cardiac disease	Umbilical hernia
Kyphosis	Hepatosplenomegaly
Failed newborn hearing screen	Frequent respiratory infection
Orthopedic deformities	

From: Kingma *et al.* JIMD 2021



From: Kingma *et al.* In: PhD Thesis – MPS I: Early Diagnosis, and Treatment of Bone Disease, Introduction



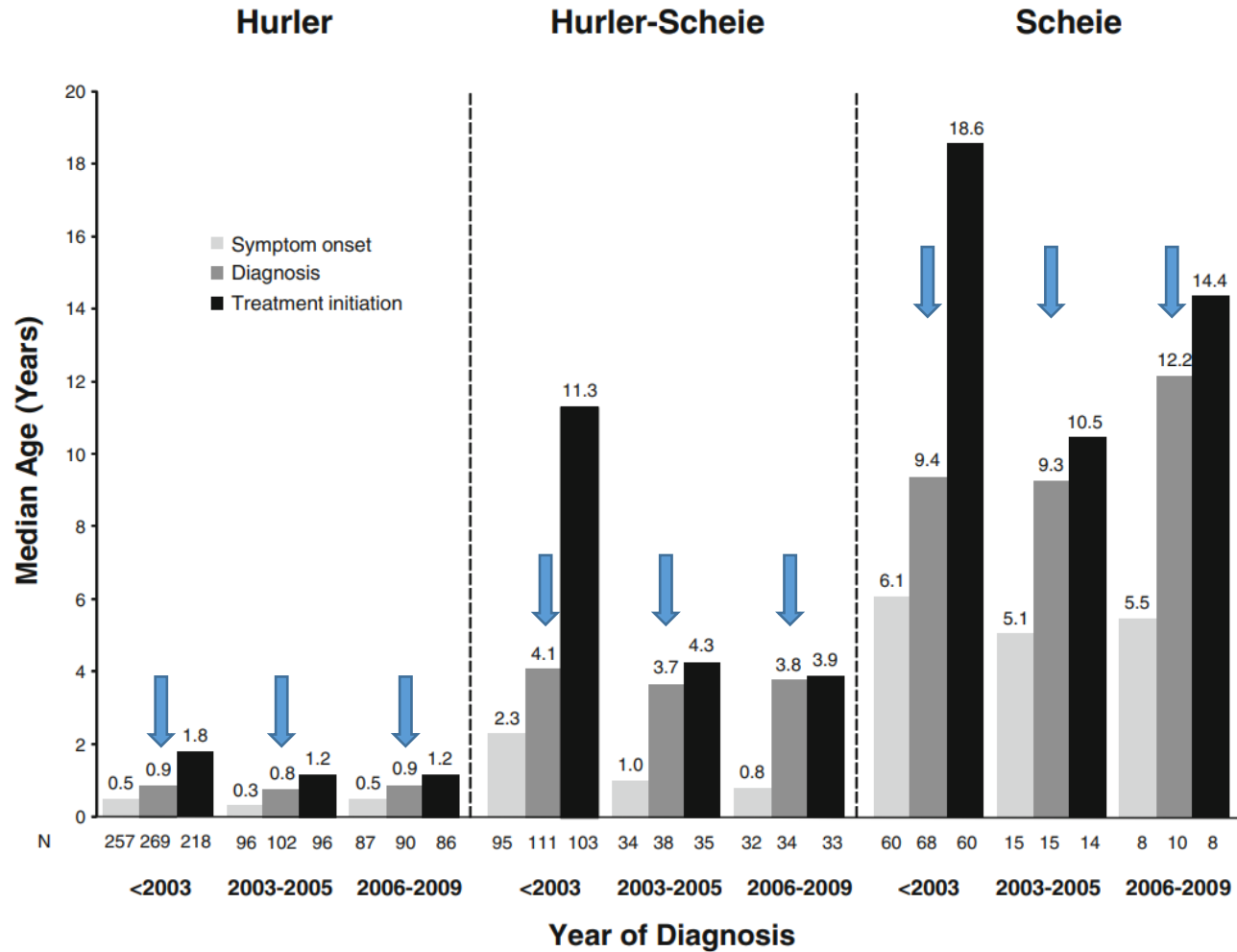
Age: 16 months



Age: 3 months

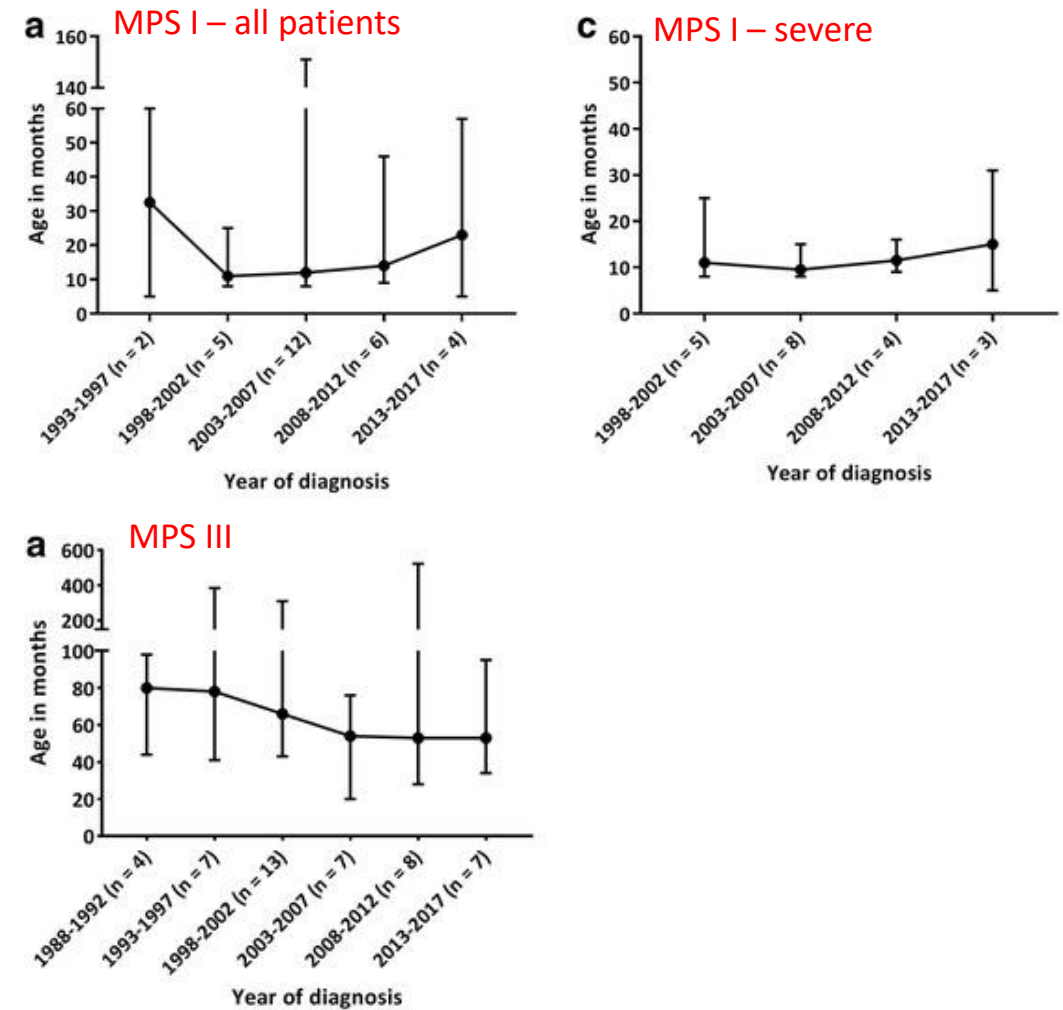
From: Parini *et al.* Acta Paediatrica 2018

Diagnostic delay: not improving

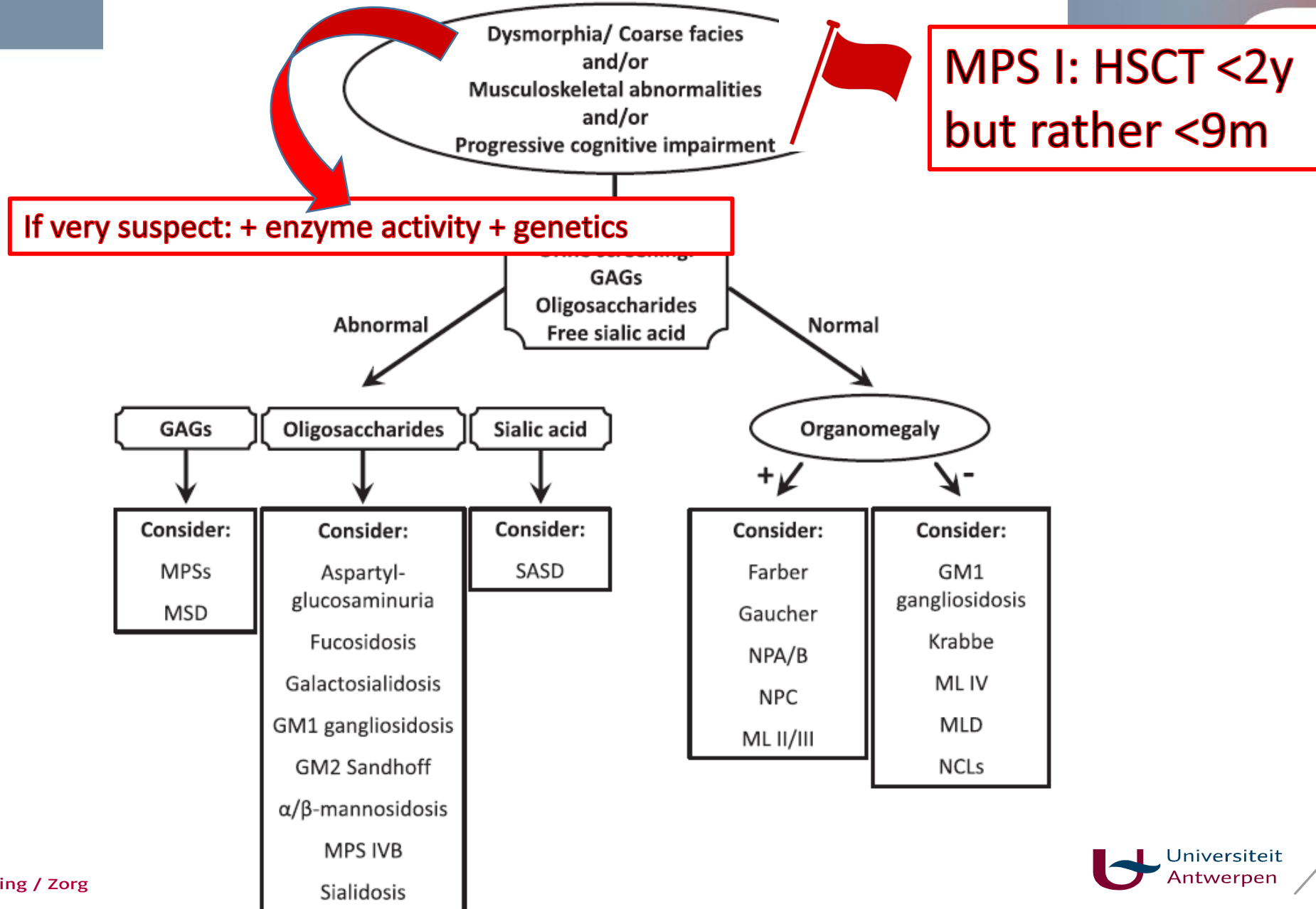


Median age at symptom onset, diagnosis, and initiation of treatment.
From: D'Aco *et al.* Eur J Ped 2012

Age at diagnosis



From: Kuiper *et al.* Orphanet J Rare Dis 2018



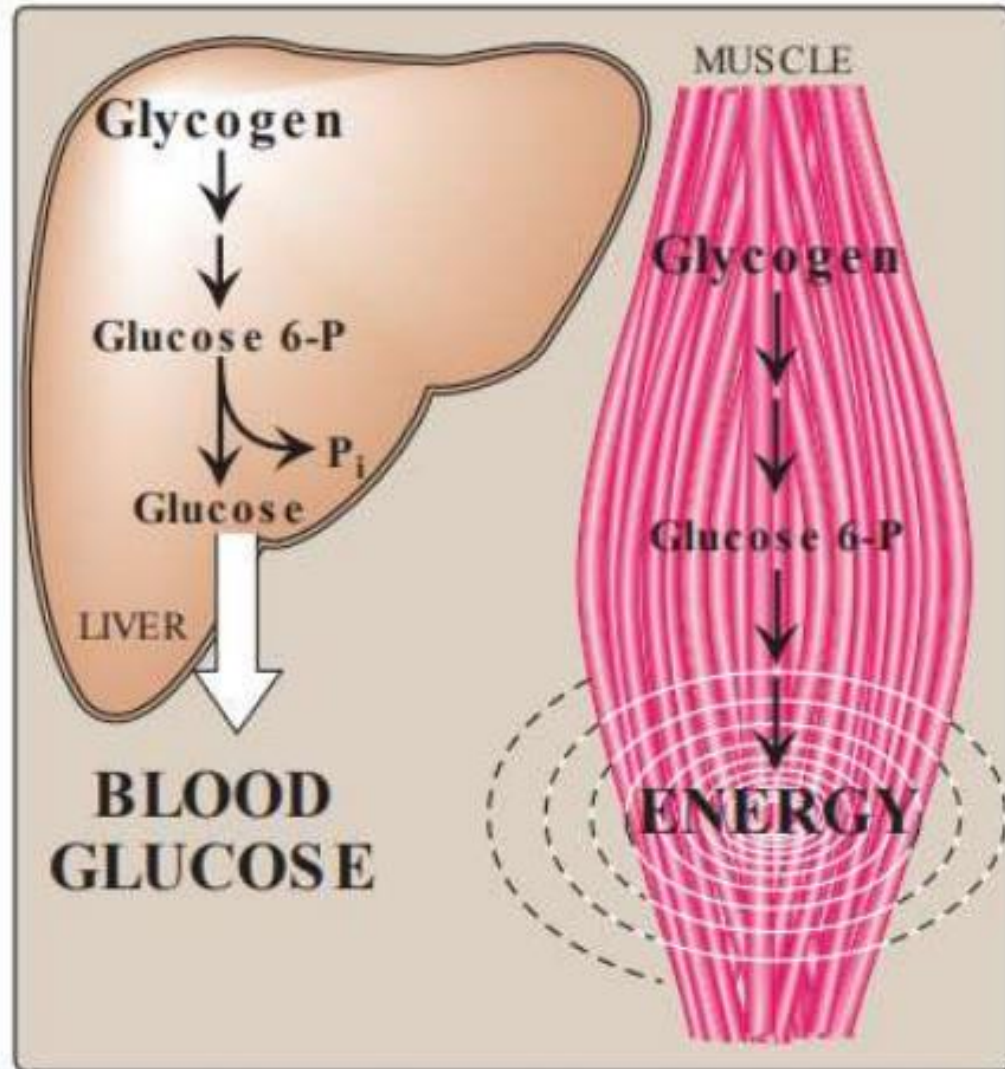
Mucopolysaccharidoses - diagnosis

- Laboratory:
 - Biomarkers: high glycosaminoglycan excretion urine (with abnormal electrophoresis, **MPS I: HS and DS**)
 - Decreased activity of lysosomal enzyme (**MPS I: α -L-iduronidase deficiency**)
 - Genetics: genes coding for lysosomal enzymes (**MPS I: *IDUA***)
- X-rays: dysostosis multiplex
- Ultrasound heart: thickening mitral/aorta valve, LVH
- MRI brain: white matter lesions, ventricular dilatation
- Ophthalmologic: corneal clouding, glaucoma

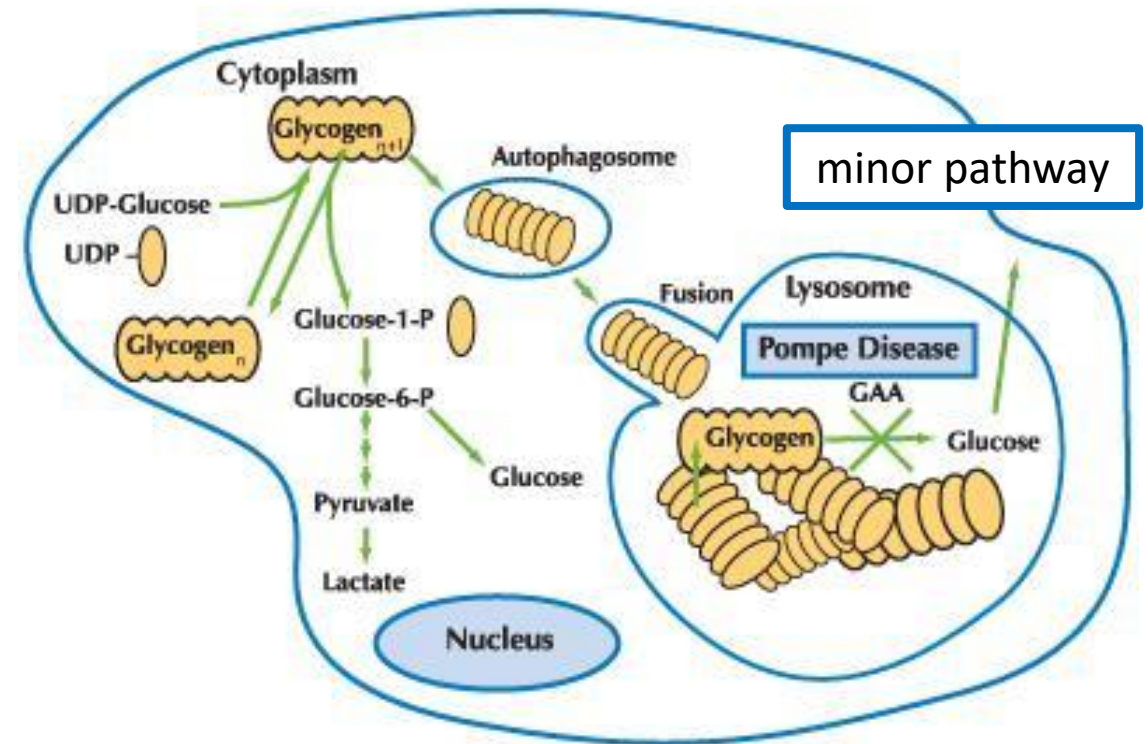
The background of the slide features a photograph of a modern, multi-story building with a facade of large glass windows. Some of the windows are tinted in various colors like blue, green, and red. The building is partially obscured by a semi-transparent light blue overlay on the left and a large red and white geometric graphic on the bottom right. The text "Pompe disease" is centered over the building image.

Pompe disease

Pompe disease - physiology

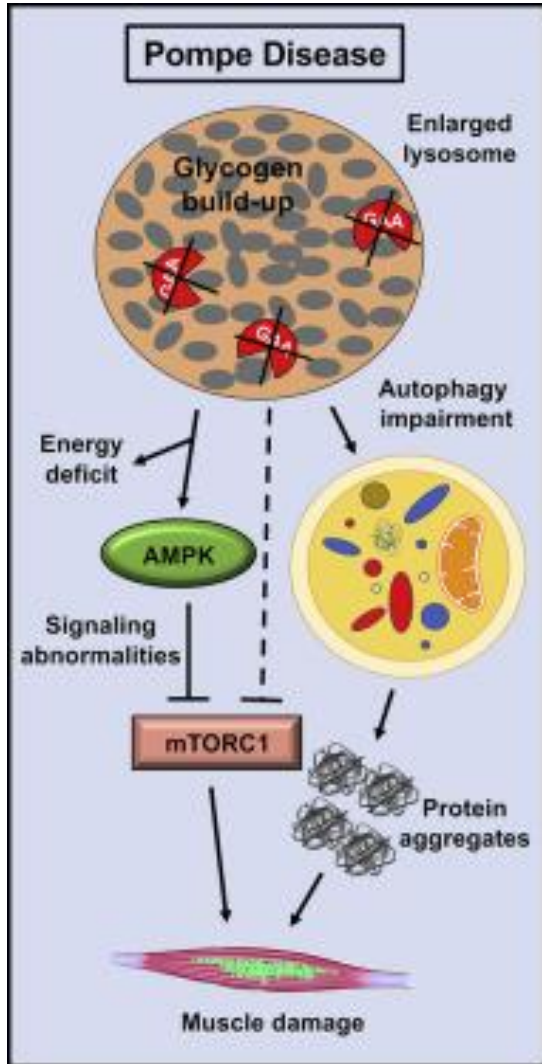


<https://www.pharmacy180.com/article/structure-and-function-of-glycogen-1883/>



<https://www.unitedpompe.com/about-pompe-disease/>

Pompe disease - pathophysiology



α -glucosidase (GAA) deficiency:

- GAA required for glycogen breakdown in lysosome
- Deficiency → glycogen accumulation in:
 - skeletal muscle, cardiac muscle (metabolic disorder, muscular disorder)
 - motor neurons (neuromuscular disorder)

Consequences of storage:

- Lysosomal enlargement causing mechanical disruption of the myofibrillar architecture
- Impaired autophagy and energy metabolism
- Secondary damage to motor neurons resulting in progressive muscle weakness

Pompe disease – clinical manifestations



Hypotonia and
respiratory insufficiency

<https://agsd.org.uk/wp-content/uploads/2019/04/infantile-pompe-guide.pdf>

Kennis / Ervaring / Zorg

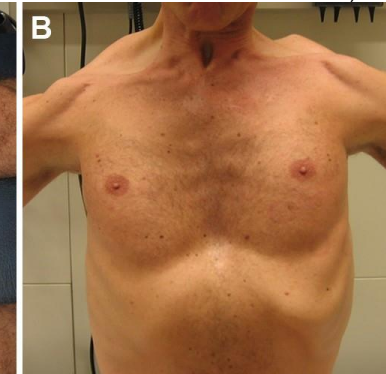


Abnormal support on thighs
Scapular winging

Nikitin et al. Clinical examination of patients with late-onset Pompe disease: typical and not typical symptoms and signs. *Neuromuscular Diseases* 2020;9:26-33

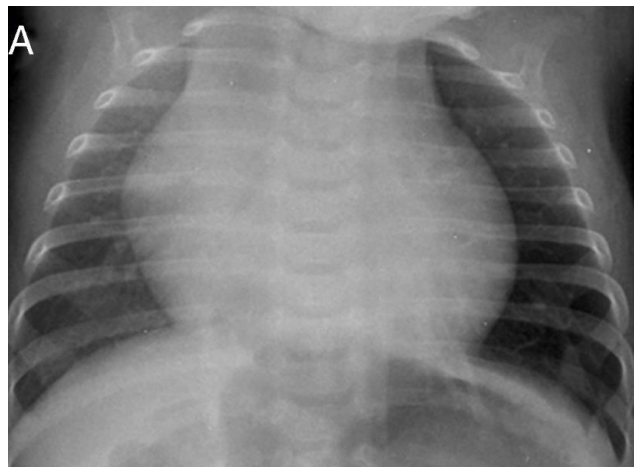
Atrophy of the quadriceps muscle (A),
Muscle atrophy and scapular winging (B),
Ptosis (C)

Van der Beek et al. Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. *Orphanet J Rare Dis* 2012;7:88



Cardiomegaly and cardiomyopathy

Bonilla-Palomas et al. When should we start enzyme replacement therapy for infantile Pompe disease with severe cardiomyopathy? *Rev Esp Cardiol (Engl Ed)*. 2012;65:100-2



Pompe disease - diagnosis

- Blood: Increased CK, LDH, AST
- Urine: increased glucose tetrasaccharide
- Decreased α -glucosidase enzyme activity (bloodspot)
- Abnormalities ECG, heart ultrasound, X-ray: cardiomyopathy

Genetics:

- Autosomal recessive
- >300 pathogenic variants in *GAA*
- CRIM status (cross-reactive immunologic material), important for therapy decisions
 - Genetics
 - Variants leading to absent protein production are usually CRIM- → antibody production → reduced response.
 - Missense variants and late truncating variants usually produce a stable but non-functional protein → CRIM+
 - Western blot isolated lysosomal GAA (fibro/leuko/muscle)

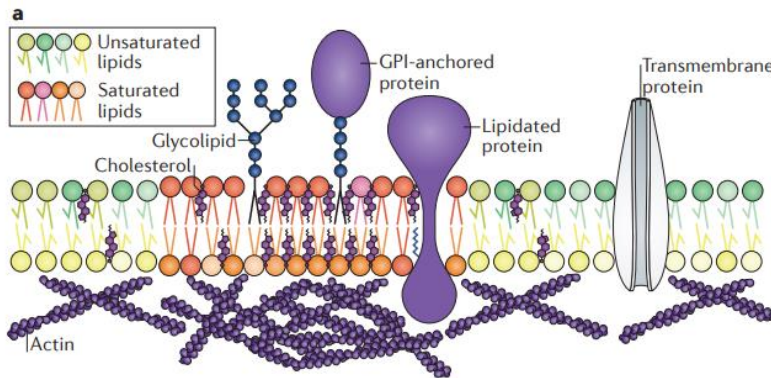
A modern, multi-story building with a glass facade featuring colorful vertical stripes in shades of blue, green, and red. The building is partially obscured by a semi-transparent light blue overlay on the left and a semi-transparent red overlay on the right. The text "Gaucher disease" is centered over the image in a black, italicized serif font. The background shows a clear blue sky with some clouds and green foliage in the top right corner.

Gaucher disease

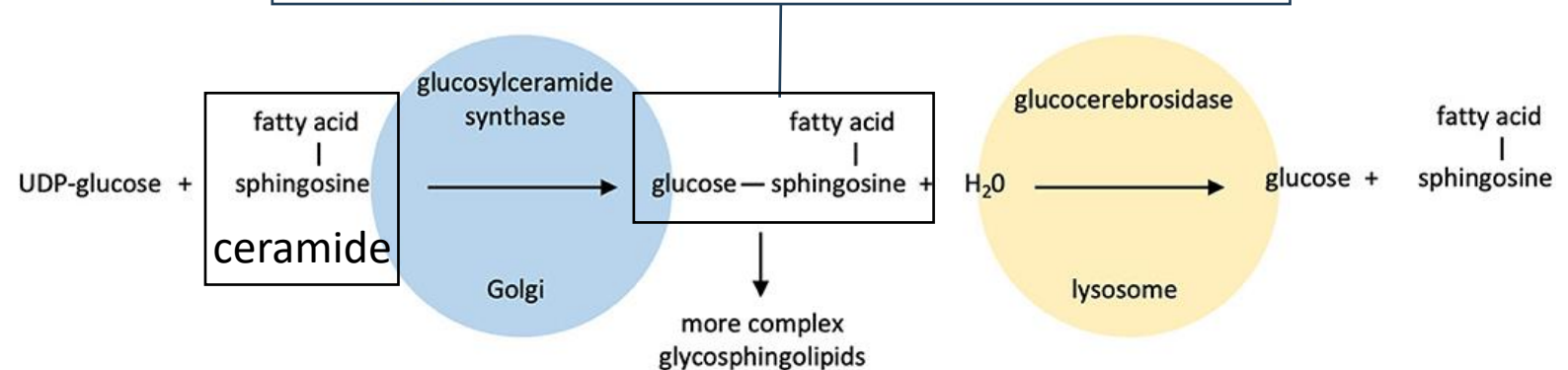
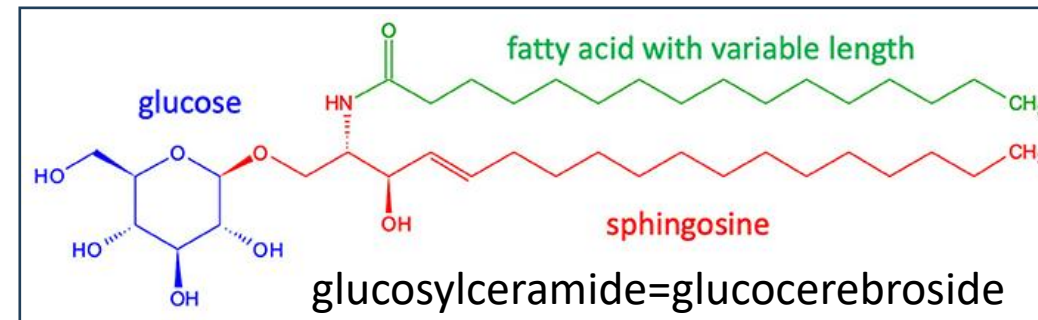
Gaucher disease - physiology

Many membrane lipids, such as sphingolipids: structural roles, but also important signaling function
Structures appear complex, but built from a few recurring core components

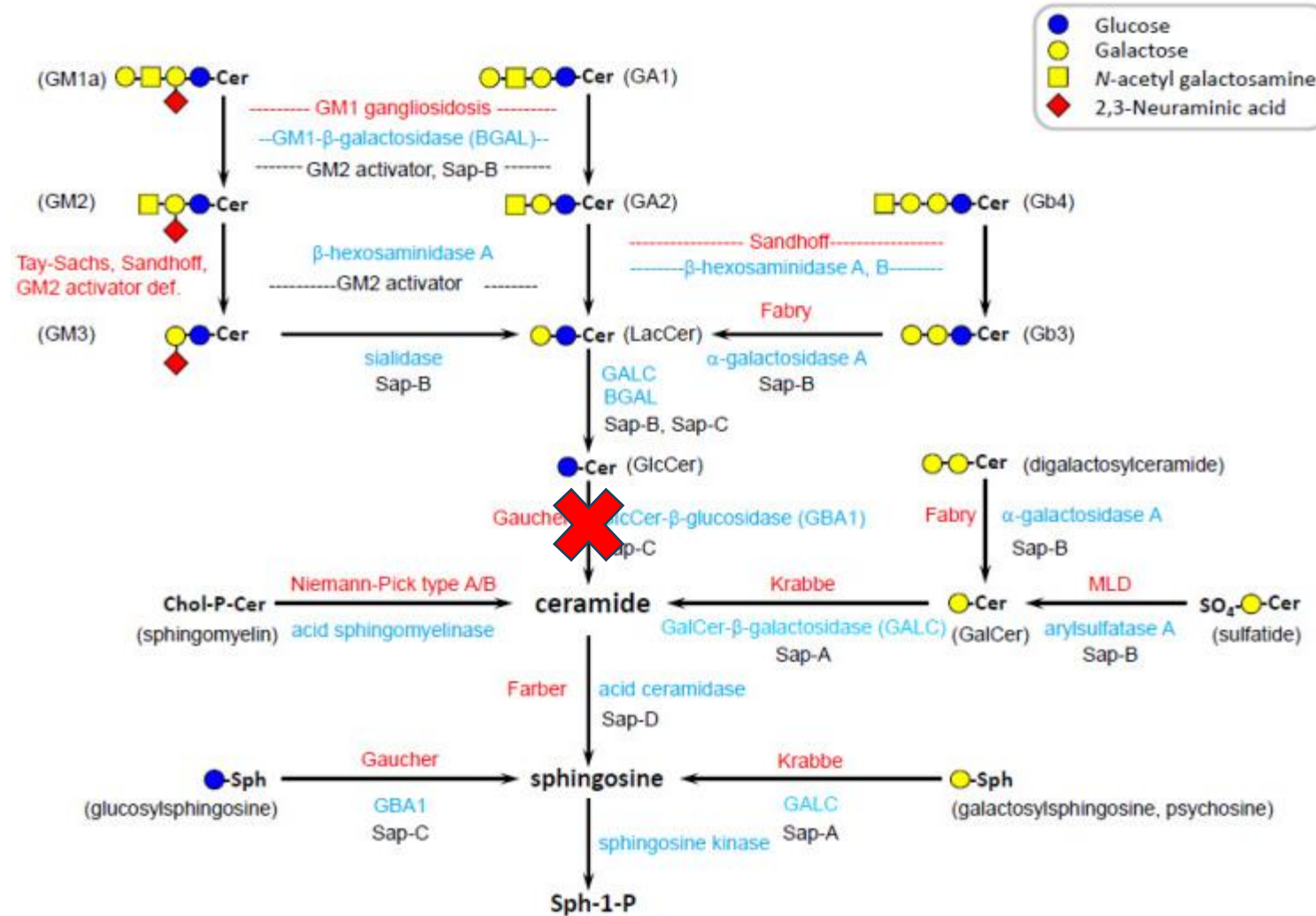
- Sphingosine: fundamental building block, amino-alcohol with long unsaturated hydrocarbon chain (intermediate in ER → processed in Golgi)
- Ceramide: sphingosine attached to fatty acid → other glycosphingolipids, including glucocerebroside (substrate in GD)



Sezgin, E., Levental, I., Mayor, S. *et al.* The mystery of membrane organization: composition, regulation and roles of lipid rafts. *Nat Rev Mol Cell Biol* **18**, 361–374 (2017). <https://doi.org/10.1038/nrm.2017.16>



Gaucher disease – (patho)physiology



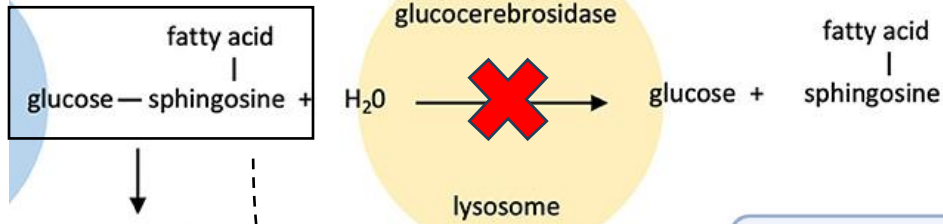
Clinical effect depending on:

- Type substrate
- Degree accumulation
- Type tissue
- Sensitivity tissue

Matsuda J, Tsuboi K, Yoneshige A. Analysis of sphingolipid activator protein activity for sphingolipid hydrolases. 2021 Sep 28 [Updated 2022 Mar 16]. In: Nishihara S, Angata K, Aoki-Kinoshita KF, et al., editors. Glycoscience Protocols (GlycoPODv2) [Internet]. Saitama (JP): Japan Consortium for Glycobiology and Glycotechnology; 2021-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK593926/>

Gaucher disease - pathophysiology

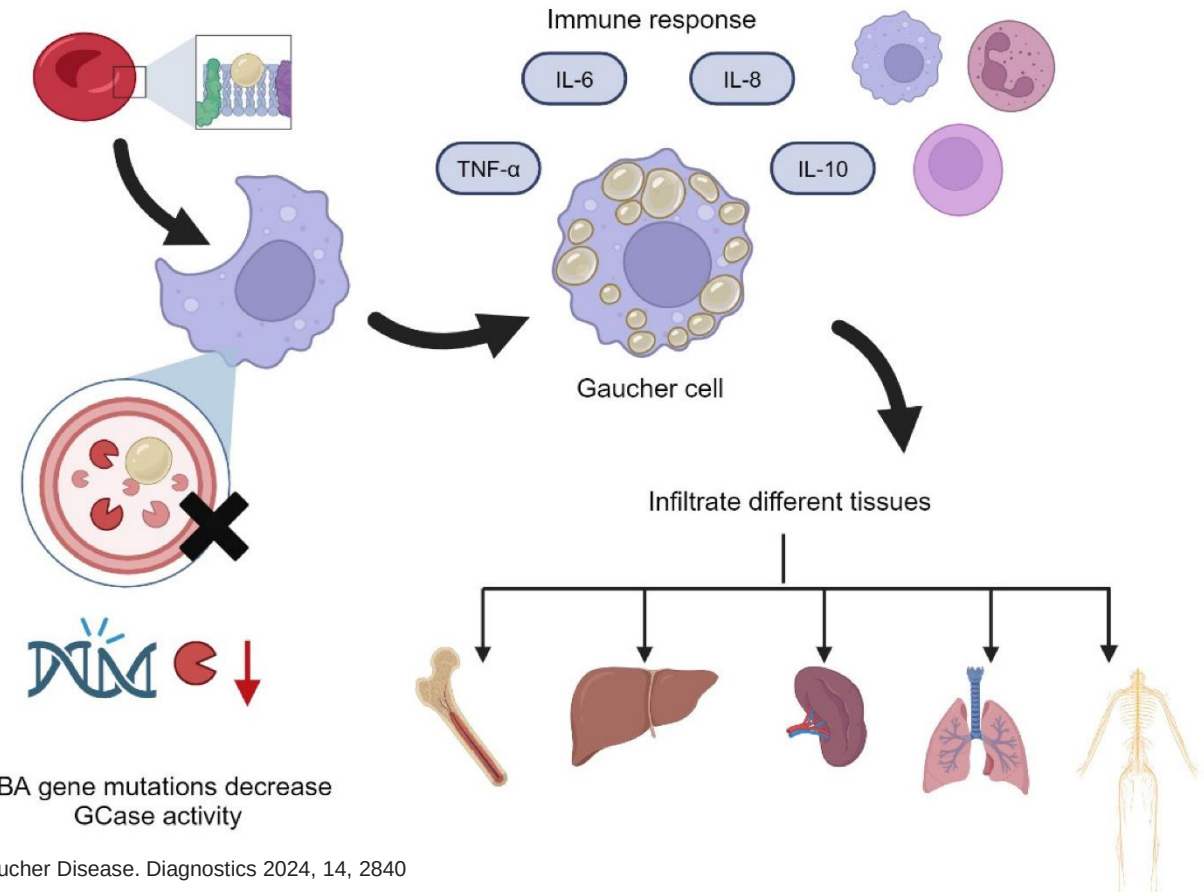
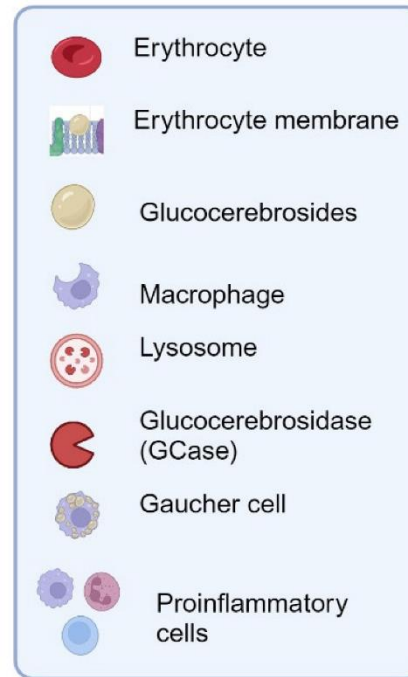
glucosylceramide=
glucocerebroside



more complex
glycosphingolipids

Edited from: Desplanque M et al. Trends in Glucocerebrosides Research: A Systematic Review. Front Physiol. 2020;11:558090

glucosylsphingosine
(soluble, toxic)



Gaucher disease – clinical manifestations

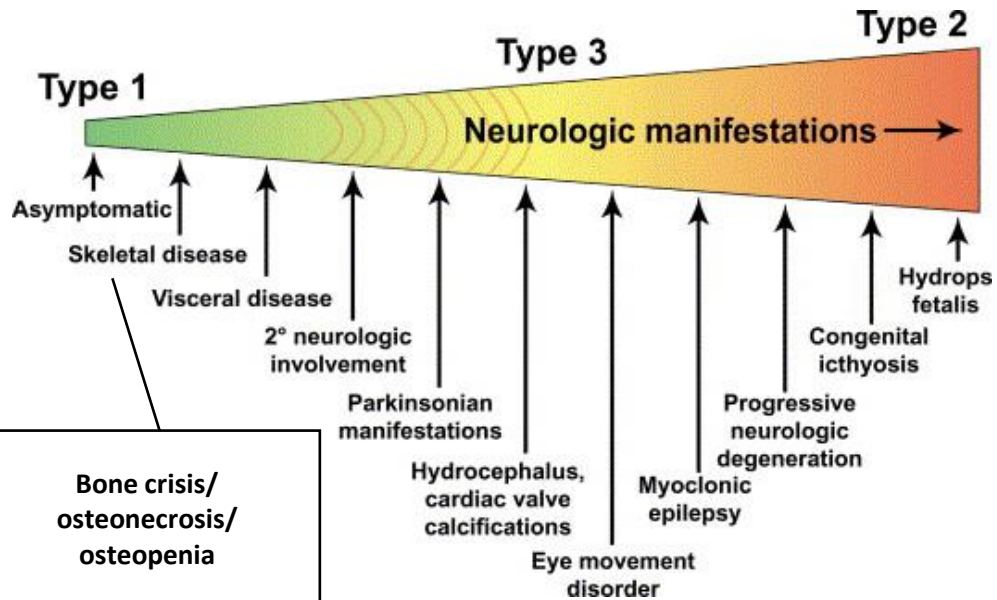
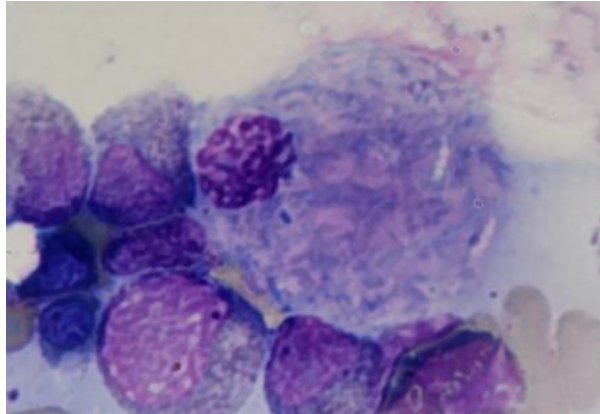
Erlenmeyer flask deformation



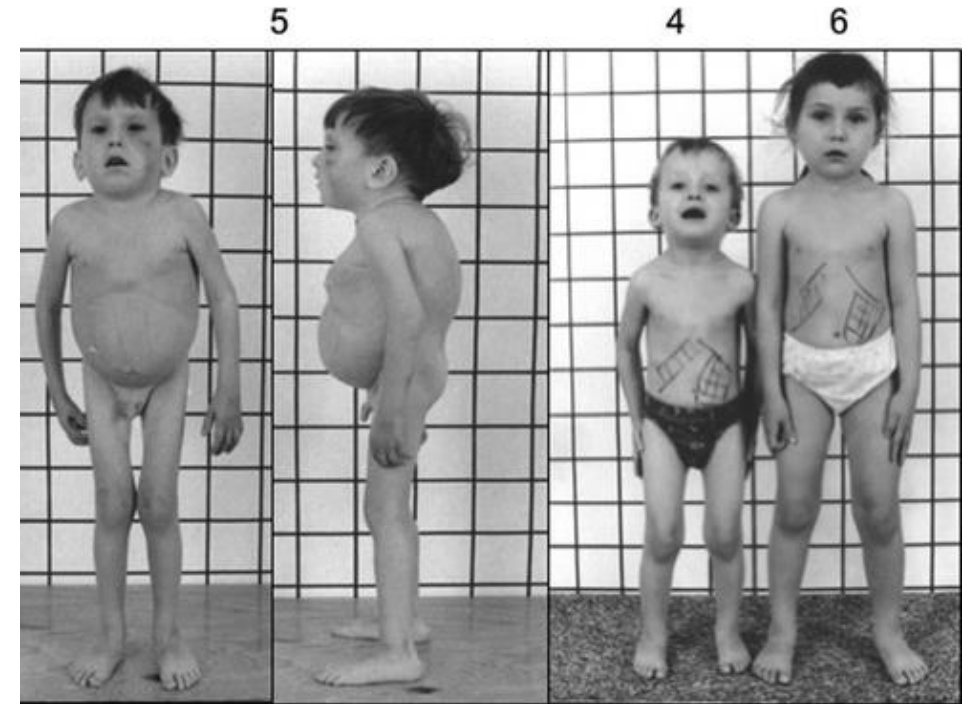
Kaplan P et al.
Revised
recommendations
for the
management of
Gaucher disease in
children. Eur J
Pediatr.
2013;172:447-58

<https://imagebank.hematology.org/image/64378/gaucher-cells>

Gaucher cells bone marrow



Sidransky E. Gaucher disease: complexity in a "simple" disorder. Molecular Genetics and Metabolism 2004;83:6-15



Patient 10

Patients 15 and 16

Tylki-Szymańska et al. Characterization of neuronopathic Gaucher disease among ethnic Poles. Genet Med 2006;8,8-15



**Splenomegaly with/without hepatomegaly
Trombocytopenia/anemia**

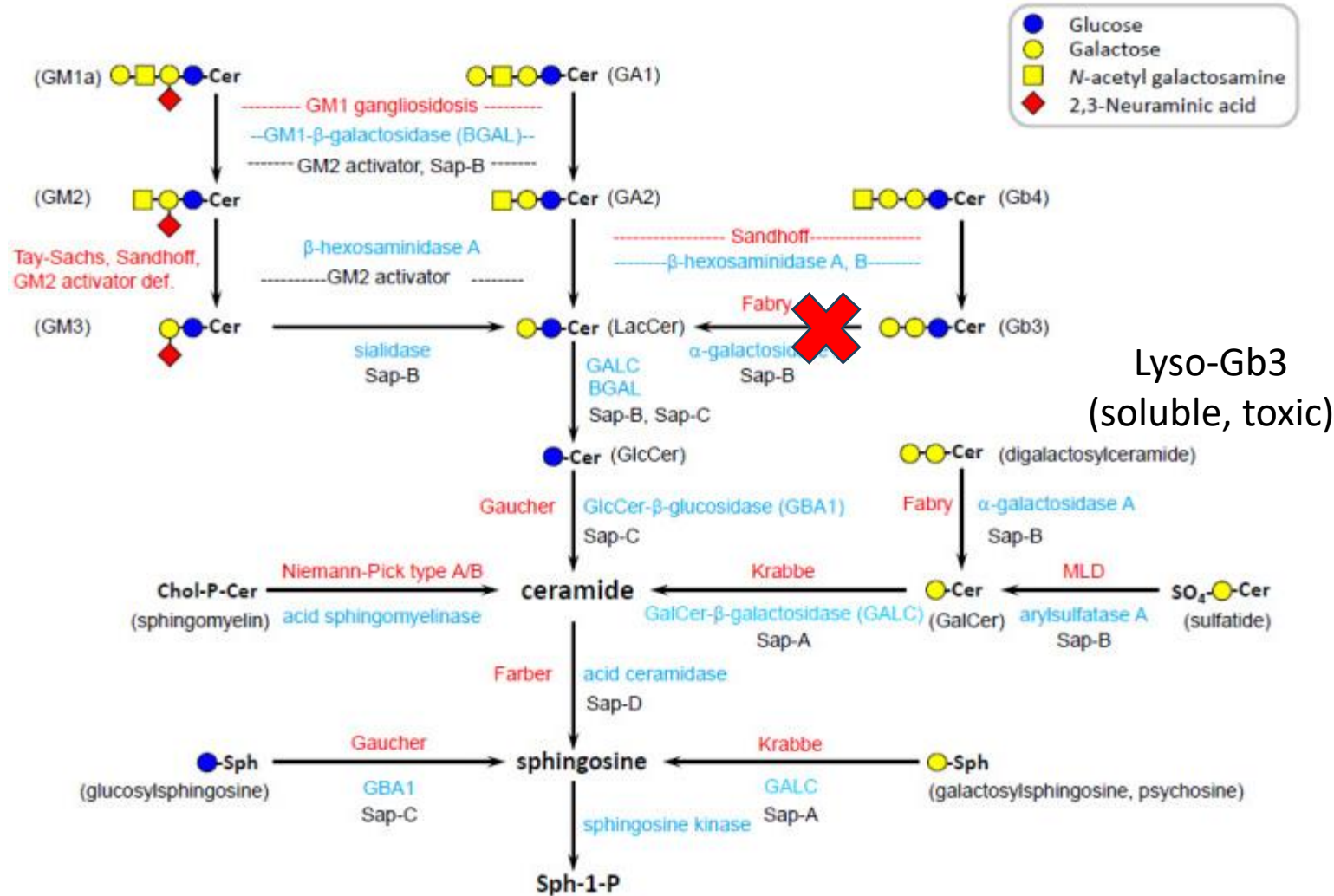
Gaucher disease - diagnosis

- Laboratory:
 - General: thrombocytopenia, anemia, high ferritin
 - Gaucher cells in bone marrow
 - Biomarkers: extremely high chitotriosidase (macrophage activation marker), glucosylsphingosine (Lyso-Gb1)
 - Decreased β -glucocerebrosidase-activity
 - Acid sphingomyelinase (DD: ASMD/Niemann Pick A/B)
 - Genetics: *GBA1* variants (*SMPD1*; DD: ASMD/Niemann Pick A/B)
- Ultrasound of the abdomen: spleen and liver enlargement
- DEXA scan: osteopenia



Fabry disease

Fabry disease – (patho)physiology



Lyso-Gb3
(soluble, toxic)

Clinical effect depending on:

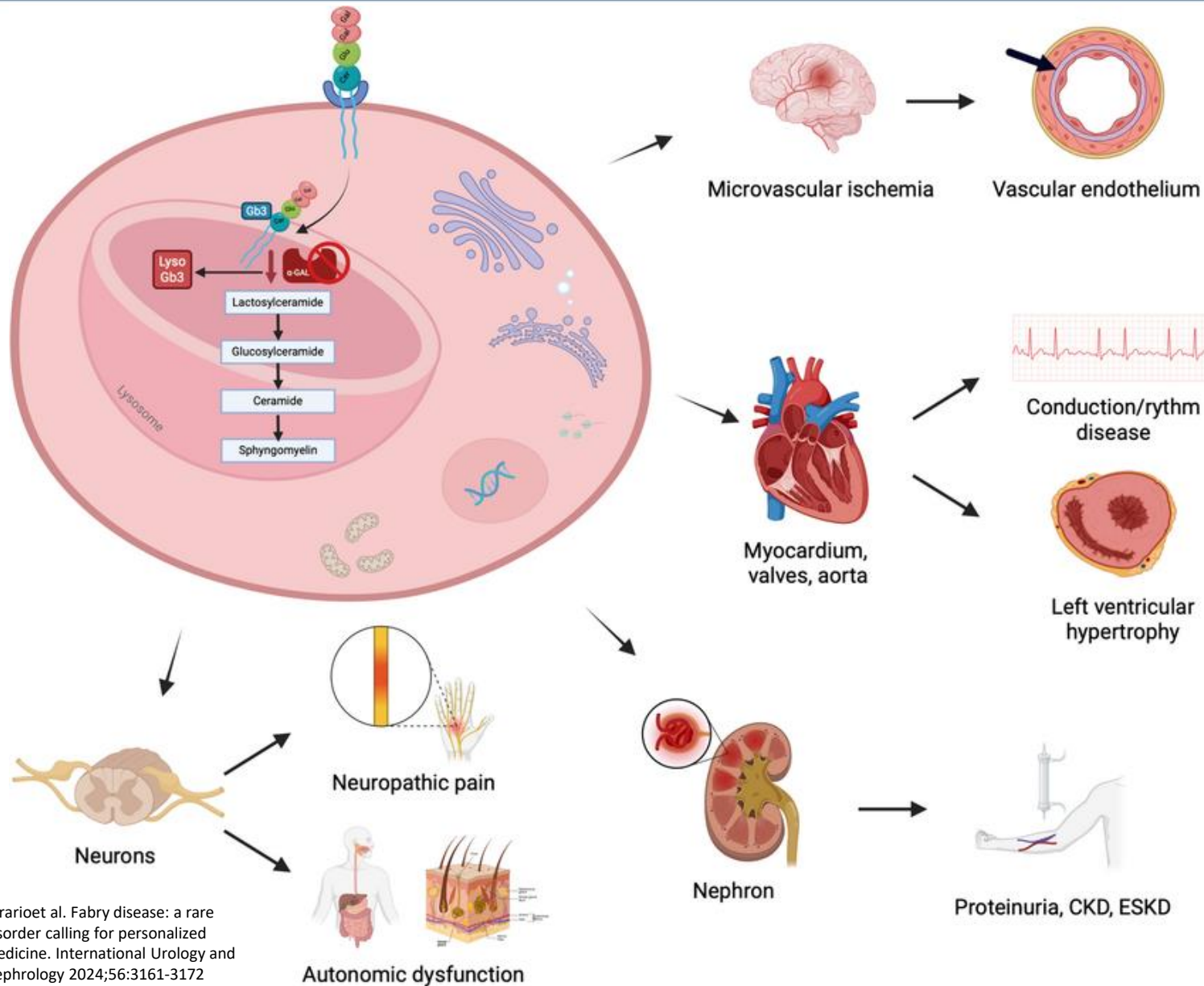
- Type substrate
- Degree accumulation
- Type tissue
- Sensitivity tissue

Fabry disease:

- X-linked *GLA*
- α-galactosidase A deficiency
- Globotriaosylceramide (Gb3) accumulation in tissue →
- De-acylation (acylgroup/fattyacid group lysed) by acid ceramidase → circulating toxic Lyso-Gb3

Matsuda J, Tsuboi K, Yoneshige A. Analysis of sphingolipid activator protein activity for sphingolipid hydrolases. 2021 Sep 28 [Updated 2022 Mar 16]. In: Nishihara S, Angata K, Aoki-Kinoshita KF, et al., editors. Glycoscience Protocols (GlycoPODV2) [Internet]. Saitama (JP): Japan Consortium for Glycobiology and Glycotechnology; 2021-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK593926/>

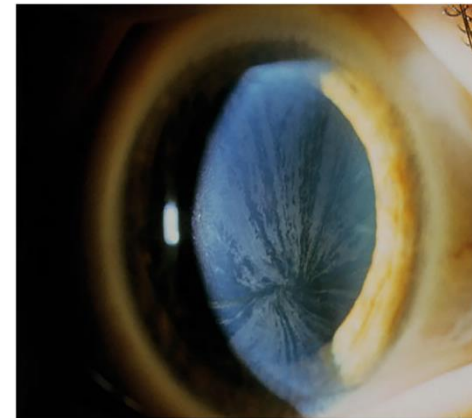
Fabry disease - pathophysiology



- Gb3 and Lyso-Gb3 →
 - Endothelial cells (blood vessels throughout the body)
 - Kidney cells – podocytes, glomerular endothelium, distal tubules
 - Heart – cardiomyocytes and vascular endothelium
 - Peripheral nervous system – nerve endings
 - Smooth muscle (GI tract, vascular media)
 - Sweat glands
- Females (X-inactivation) mostly fewer symptoms

Fabry disease - diagnosis

- Laboratory:
 - General: proteinuria, high eGFR (hyperfiltration), later high creatinine
 - Biomarkers: high globotriaosylsphingosine (Lyso-Gb3; males and females)
 - Decreased α -galactosidase A activity (males)
 - Genetics: *GLA* variant
- Ultrasound heart: LVH
- MRI brain: white matter lesions
- Ophthalmologic: cornea verticillata
- Dermatologic: angiokeratomas



Wasielica-Poslednik et al. Influence of Corneal Opacity on Intraocular Pressure Assessment in Patients with Lysosomal Storage Diseases. PLOS ONE 2017;12:e0168698



<https://www.fabrydisease.org/images/article-images/angiokeratoma-12.jpg>

Take home messages

- Lysosomal storage disorders share a common mechanism—substrate accumulation—but present with highly diverse clinical phenotypes.
- Early recognition is critical, for instance:
 - Coarse facies and bone abnormalities
 - Splenomegaly and thrombocytopenia
 - Hypotonia and cardiomegaly
 - Multisystem involvement (heart, kidney, brain, bone, muscle) should trigger suspicion.
- MPS, Pompe, Gaucher, and Fabry are clinically and biochemically distinct:
 - Diagnosis: targeted enzyme assays, disease-specific biomarkers, genetic confirmation
 - Other LSDs mostly genetic diagnosis
 - Timely initiation of disease-specific therapy (ERT, chaperones, substrate reduction) can dramatically alter disease progression.

sandra.kingma@uza.be



Monday therapie day 🙌

