Medical follow-up and current treatment on the different MPS-types

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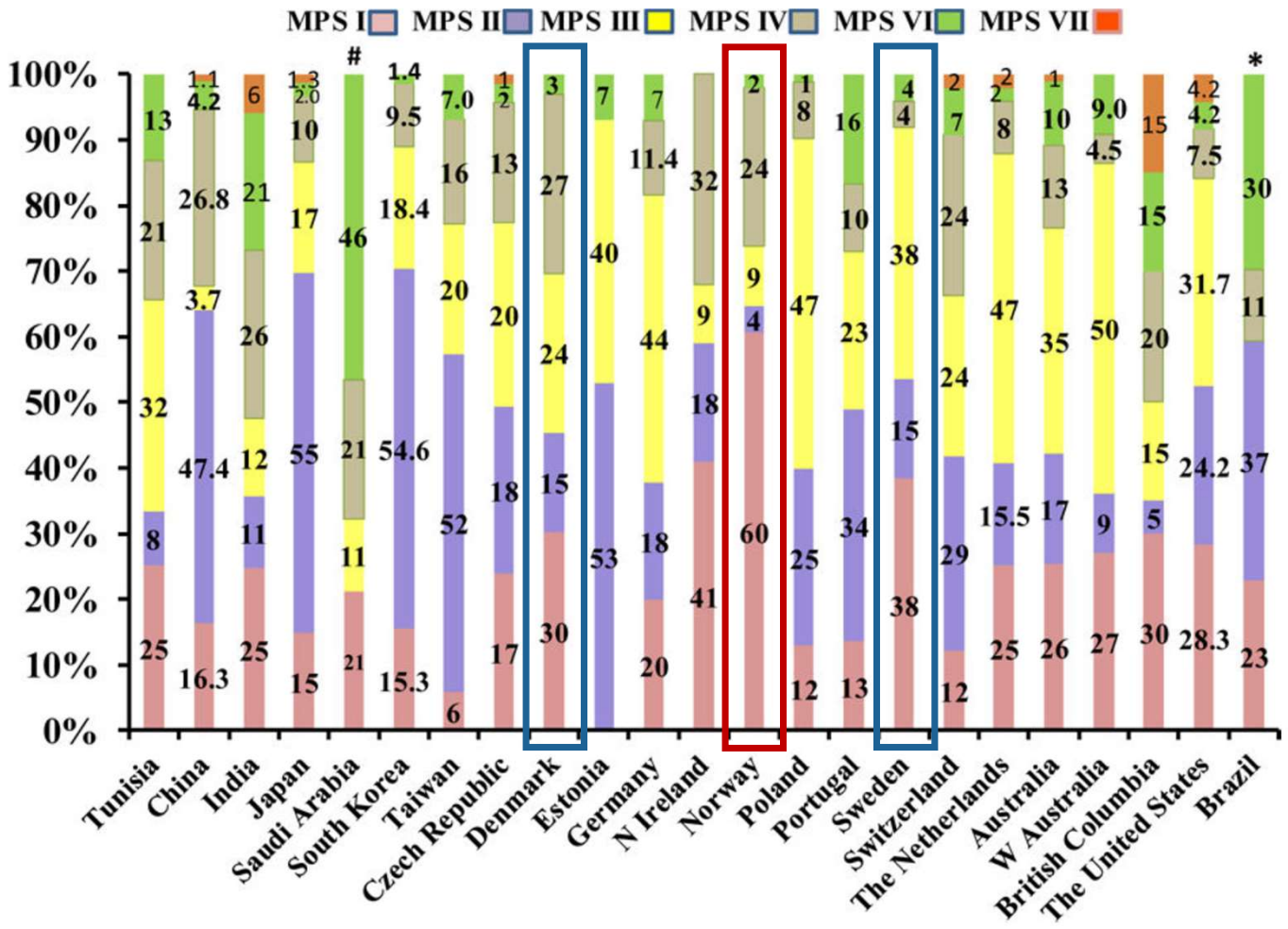
  - BioMarin
  - Chiesi
  - Amicus
  - Alexion
  - Sanofi
  - Takeda

Mainz

Gießen

Epidemiology



Norway (data collection 1979-2004) 5,4 Mio
45 MPS cases (3.08: 100,000 live births)
- **MPS I: 60%**
- MPS IV 24%
- MPS III 9%
- MPS II 4%
- MPS VI 2%

Schweden (data collection 1975-2004) 10,4 Mio
52 MPS cases (1.75: 100,000 live births)
- **MPS I: 38%**
- MPS III: 38%
- MPS II: 15%
- MPS IV: 4%
- MPS VI: 4%

Denmark (data collection 1975-2004) 5,8 Mio
33 MPS cases (1.77: 100,000 live births)
- **MPS I: 30%**
- MPS IV: 27%
- MPS III: 24%
- MPS II: 15%
- MPS VI: 3%

Khan SA, Peracha H, Ballhausen D, Wiesbauer A, Rohrbach M, Gautschi M, Mason RW, Giugliani R, Suzuki Y, Orii KE, Orii T, Tomatsu S. Epidemiology of mucopolysaccharidoses. Mol Genet Metab. 2017 Jul;121(3):227-240.

MPS classification

MPS type	Eponym(s)	Enzyme deficiency	GAG stored	CNS involvement	Treatment
MPS I	Hurler	alpha-L-iduronidase	DS,HS	+ / - CNS involvement	HSCT, (ERT)
	Hurler-Scheie		DS,HS		HSCT or ERT
	Scheie		DS,HS		ERT
MPS II	Hunter type A Hunter type B	Iduronate-2-sulfatase	DS,HS	+ / - CNS involvement	ERT, (HSCT)
MPS III	Sanfilippo A	Heparan N-sulfatase	HS	**Mainly** CNS involvement	no
	Sanfilippo B	alpha-N-acetylglucosaminidase	HS		
	Sanfilippo C	Acetyl-CoA: alpha glucosaminide Acetyltransferase	HS		
	Sanfilippo D	N-acetylglucosamine-6-sulfatase	HS		
MPS IV	**Morquio A**	**N-acetyl-galactosamine-6-sulfatase**	**KS,CS**	No CNS involvement	ERT
	Morquio B	alpha-galactosidase	KS		
MPS VI	**Maroteaux-Lamy**	**Arylsulfatase B or ASB**	**DS**		ERT, (HSCT)
MPS VII	Sly	Alpha glucuronidase	DS,HS,CS	+/ - CNS involvement	ERT
MPS IX	Hyaluronidase Def.	Hyaluronoglucosaminindase-1	HA	No CNS involvement	no

CS, chondroitin sulfate, DS, dermatan sulfate; ERT, enzyme replacement therapy; GAG, glycosaminoglycan; HA, hyaluronan; HS, heparan sulfate; KS, keratan sulfate; MPS, mucopolysaccharidoses.

Neufeld EF, Muenzer J. *The mucopolysaccharidoses*. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. Vol 3. 8th ed. New York: McGraw-Hill; 2001:3421–3452.

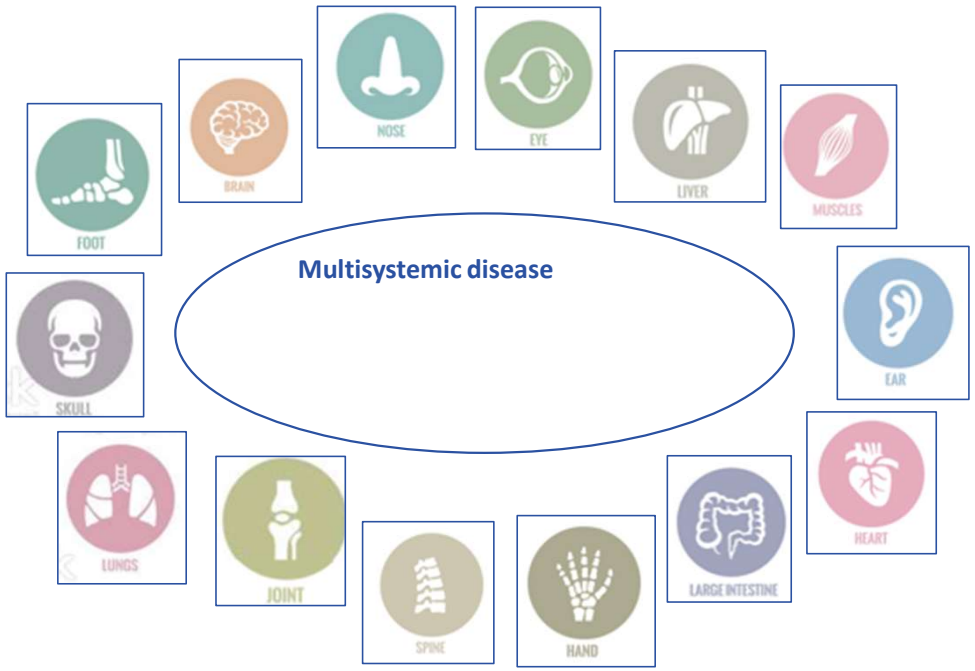
Multisystemic disease: signs and symptoms in MPS IVA and MPS VI

Appearance:
Coarse facial features
Thickened eyebrows
Macroglossia

Gastrointestinal:
Hepatosplenomegaly
Inguinal and umbilical hernia
Swallowing problems
Diarrhoea

Lung:
Narrowed upper airways
Obstructive sleep apnoea
Restrictive lung disease
Recurrent infections

Skeleton:
Dysostosis multiplex
Gibbus, kyphosis and scoliosis
Atlanto-axial instability
Joint contractures (MPS VI)
Joint hypermobility (MPS IVA)



High variability and heterogeneity in symptoms and organ involvement, but no cognitive involvement

Eyes:
Impairment of vision
Corneal clouding
Glaucoma (MPS VI)

Ears:
Hearing loss (sensorineural)
Recurrent otitis

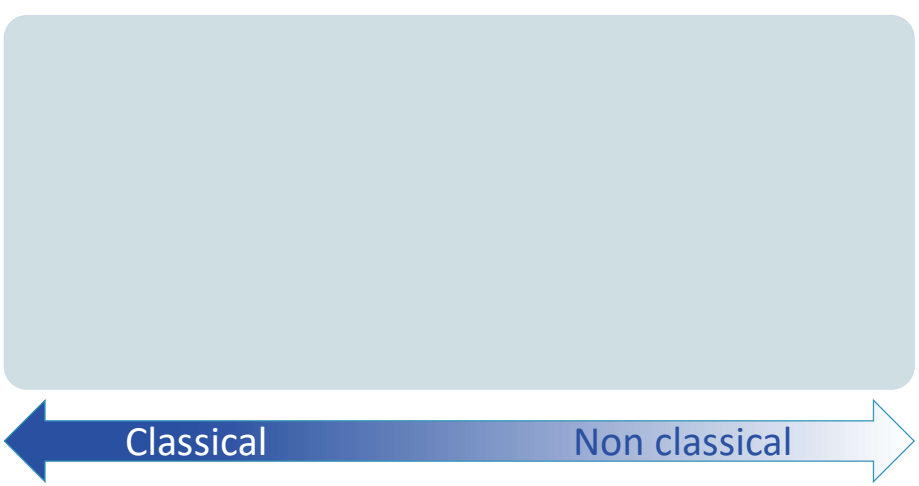
Heart:
Heart valve involvement
Cardiomegaly
Coronary disease

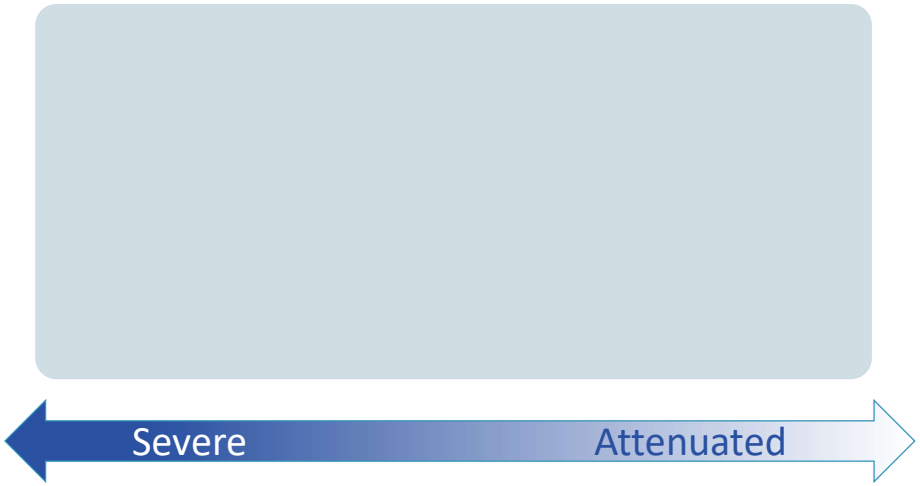
CNS:
Cervical spinal cord compression
Carpal tunnel syndrome (MPS VI)
Hydrocephalus (MPS VI)

MPS, mucopolysaccharidoses.
Wraith JE, Clarke JTR. In: Physician's Guide to the Treatment and Follow-up of Metabolic Diseases. 2006:195–203.

Spectrum of disease severity and disease progression in MPS IVA and MPS VI

- Variability in signs and symptoms
- Wide spectrum of disease severity
- Disease severity in specific organs may differ in the same patient





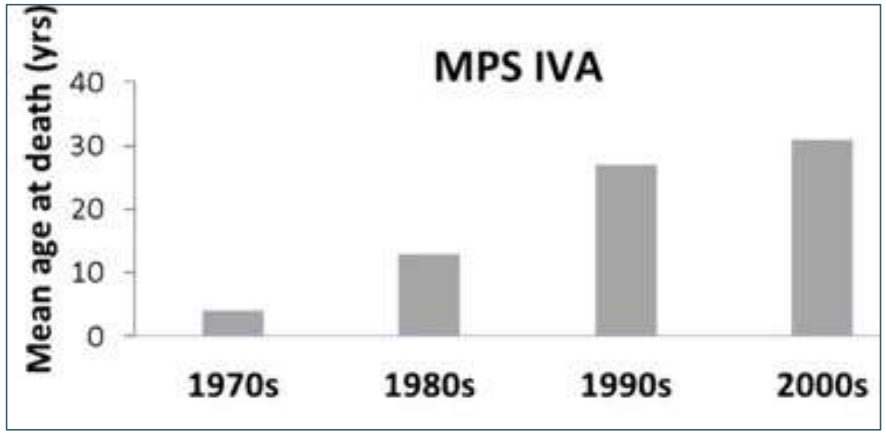
MPS, mucopolysaccharidoses.
Presenter's own images, used with the consent of the patient and/or family/caregiver where appropriate.

History of life expectancy

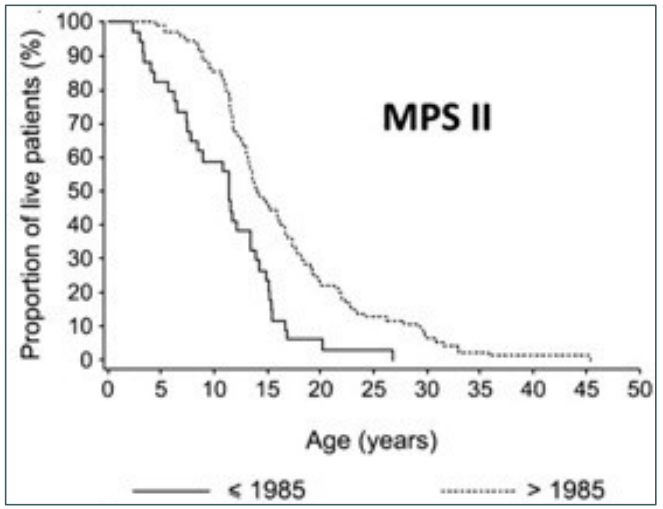
Estimates suggest that **more than 50%** of people with inherited metabolic diseases are adults, in MPS patients live beyond 20 years of age

Life expectancy in industrialized countries:

Beginning of 20th century	End of 20th century	Early 21th century	1st decade of 21st century
30-45 yrs	67 yrs Improvements in health care, nutrition, standards of living	80 yrs	In US: age ≥100 were the fastest-growing segment of the population



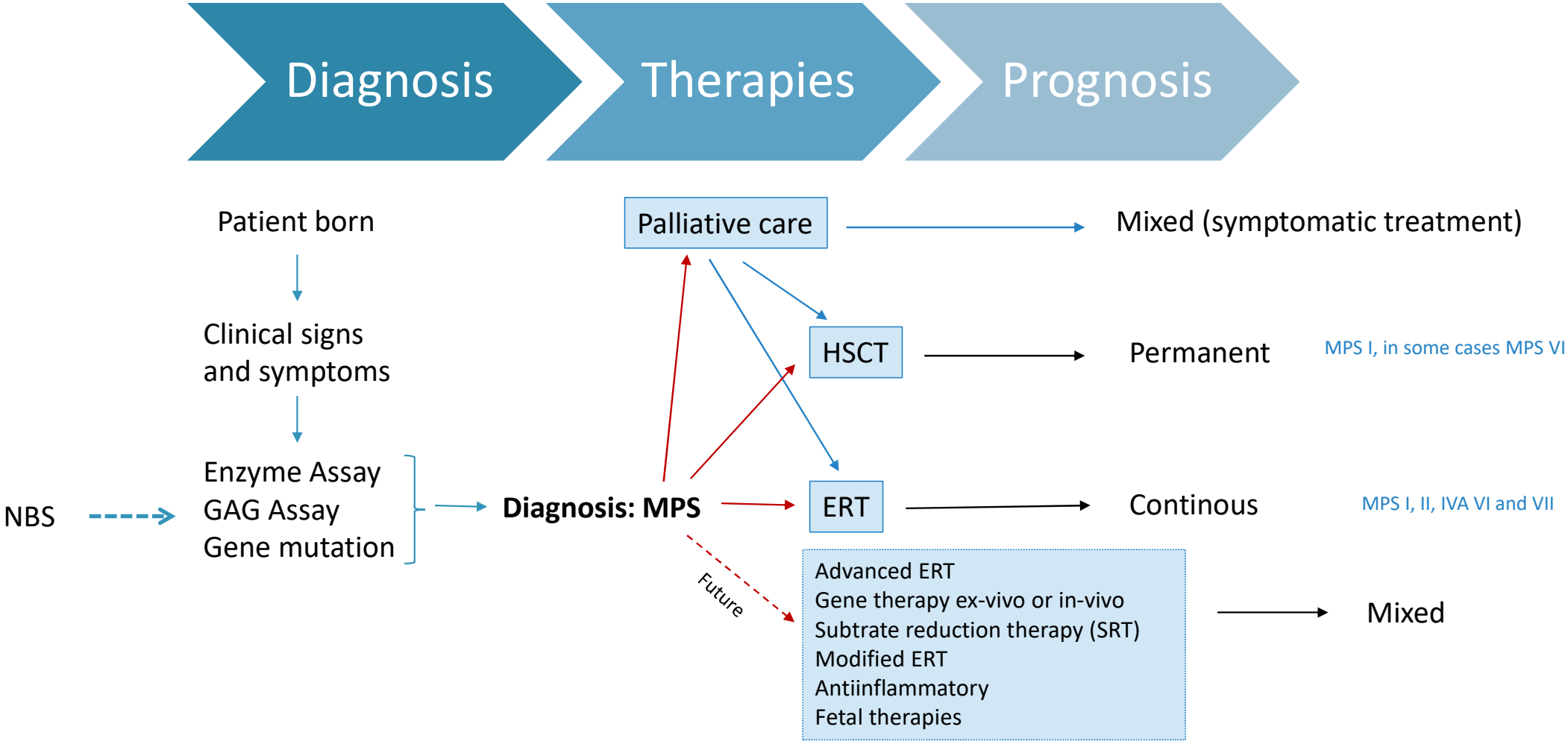
Mean age at death over time between 1975 and 2010 in patients with MPS IVA (N = 27)



Survival curves for 129 MPS II patients (HOS) according to the time period in which they died (in or before 1985 (N= 34) or after 1985 (N = 95)

Mitchell J, Berger KI, Borgo A, Braunlin EA, Burton BK, Ghotme KA, Kircher SG, Molter D, Orchard PJ, Palmer J, Pastores GM, Rapoport DM, Wang RY, White K. Unique medical issues in adult patients with mucopolysaccharidoses. Eur J Intern Med. 2016 Oct;34:2-10.

Current and future management of MPS disorders



Stapleton M,. Critical review of current MPS guidelines and management. Mol Genet Metab. 2019 Mar;126(3):238-245.

Difficulties with current guidelines

- MPS are rare diseases

- systematic reviews are limited due to the small number of patients

  ➡ insufficient and potentially inaccurate data

- Unmet challenge: to collect systematic clinical data at both National and International levels

  ➡ the establishment of an international registration system for each type of MPS is required

- most registries are sponsored by pharmaceutical companies and access to the registry is restricted to the consultant doctors or panel members

  ➡ registry data should also be established and exchanged independent of pharmaceutical companies

Management guidelines MPS

Guideline	Authors	Year	MPS Disorder	Limitation
Mucopolysaccharidosis I: Management and treatment guidelines	Muenzer et al	2009	MPS I	Biomarin/ Genzyme sponsorship; historical grouping of phenotype severity
Guidelines for the management of MPS I	Martins et al.	2009	MPS I	Genzyme sponsorship
ERT and/ or HSCT at diagnosis with MPS I: results of a European concensus procedure	de Ru et al.	2011	MPS I	Biomarin/ Genzyme sponsorship
ERT with Laronidase for treating MPS I	Jameson et al.	2013	MPS I	Biomarin sponsorship; only consideration for patients older than 2.5. Did not consider HSCT as viable treatment option.
LSDP guidelines and application form for subsidized treatment of MPS I	Australian government sponsored	2015	MPS I	Did not consider HSCT as viable treatment option
Mucopolysaccharidosis Type II: European recommendations for the diagnosis and management of a rare disease	Scarpa et al.	2011	MPS II	Shire Human Genetic Therapies sponsorship. Lack of involvement from fields of genetics and biochemistry. Did not consider HSCT
LSDP guidelines and application form for subsidized treatment of MPS II	Australian government sponsored	2015	MPS II	Lack of consideration of palliative care options. Did not consider HSCT as viable treatment option.
Practical guidelines for the management of mucopolysaccharidosis (MPS) type II	Eto et al. Japanese government sponsored	2017	MPS II	Historical treatment of phenotype severity
Inclusions of hematopoietic stem cell transplanation of mucopolysaccharidosis type II	Brazilian government sponsored	2018	MPS II	ERT and palliative care are not mentioned.

Guideline	Authors	Year	MPS Disorder	Limitation
The international guidelines for the management of treatment of Morquio A syndrome	Hendriksz et al.	2015	MPS IVA	Biomarin sponsorship. ERT only therapeutic option consdered for patients. Did not consider HSCT as viable treatment option.
LSDP guidelines and application form for subsidized treatment of MPS IVA	Australian government sponsored	2015	MPS IVA	Limited tests of efficacy and data utilized. No data reported from surgical intervention. Did not consider HSCT as viable treatment option.
Elosulfase alfa for treating Mucopolysaccharidosis type IVA	NICE	2015	MPS IVA	Guideline to be eligibility for ERT. Lack of data for palliative care. Did not consider HSCT as viable treatment option.
LSDP guidelines and application form for subsidized treatment of MPS VI	Australian government sponsored	2015	MPS VI	Lack of palliative care consideration. Did not consider HSCT as viable treatment option.
Enzyme replacement therapy with gasulfase for mucopolsaccharidosis	Brunelli et al.	2016	MPS VI	Lack of longitudinal data, ERT was the only therapy considered, lack of accurate measures of efficacy.
Recommendations for the management of MPS VI and IVA systematic evidence and consensus-based guidance	Akyol, MU	2019	**MPS VI MPS IVA**	
Sanfilippo syndrome: consensus Guidelines for clinical care	Muschol.	2022.	MPSIII	

There are no guidelines for MPS VII, MPS IX and alpha-mannosidosis

Stapleton M,. Critical review of current MPS guidelines and management. Mol Genet Metab. 2019 Mar;126(3):238-245.

Recommendations for the management of MPS MPS IVA and MPS VI

Example for well prepared recommendations
Very useful all other MPS except MPS III
no recommendations for cognitive involvement

A modified Delphi methodology was used to reach consensus among experts

Two rounds of voting

Consensus based on a ≥75% agreement rate

Specialists included

- Anesthetists
- Bone marrow transplant/ HSCT experts
- Cardiologists
- ENT
- Geneticists
- Hand surgeons
- Neurosurgeons
- Ophthalmologists
- Orthopedic surgeons
- Pediatricians
- Pulmonologist/respiratory physicians
- Radiologists

- Metabolic specialist: ≥5 years' experience of managing patients with MPS, preferably MPS IVA or VI
- Specialist surgeons/anesthesists: ≥3 years' experience of manging patients with MPS, preferably MPS IVA or VI

Excluded due to not meeting the minimum experience threshold: †7

ENT, ear, nose, and throat; HSCT, hematopoeitic stem cell transplant, MPS, mucopolysaccharidosis

Recommendations cover five key areas of patient management

General principles for the management of MPS IVA and VI

Recommended routine monitoring and assessments in MPS IVA and VI

Interventions to support respiratory and sleep disorders

Disease-modifying interventions

- ERT
- HSCT

Anaesthesia and surgical interventions

- Anaesthesia
- Limb and spinal surgeries
- Ophthalmic surgeries
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ENT, ear, nose, and throat; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplantation; MPS, mucopolysaccharidosis.

Akyol MU et al. Orphanet J Rare Dis.2019;14:118; Akyol MU et al. *Orphanet J Rare Dis*. 2019;14:137.

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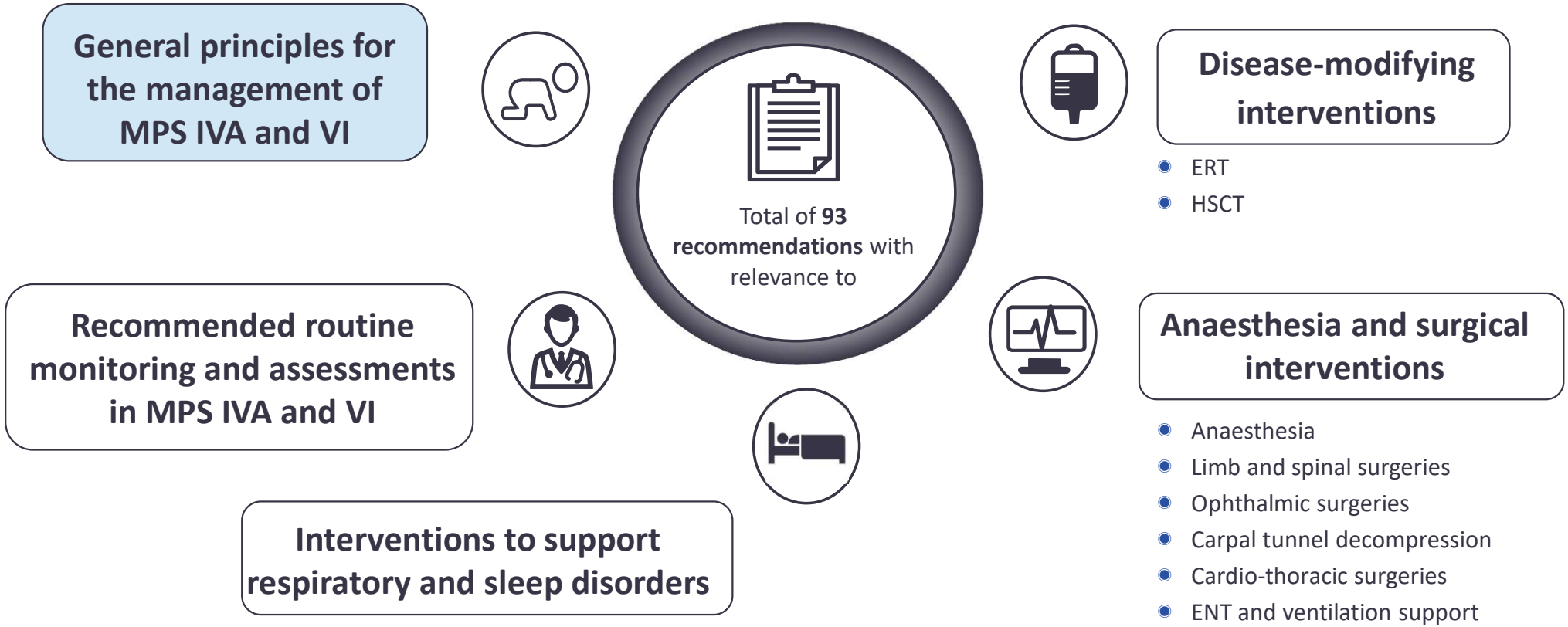
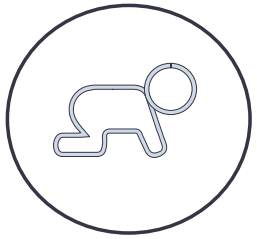


ENT, ear, nose, and throat; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplantation; MPS, mucopolysaccharidosis.

Akyol MU et al. Orphanet J Rare Dis.2019;14:118; Akyol MU et al. *Orphanet J Rare Dis*. 2019;14:137.

Early diagnosis is key to enabling prompt and appropriate management and improving outcomes



Diagnosis during infancy is critical to optimize patient outcomes

A physician with MPS experience should conduct the first consultation following diagnosis

"The first consultation should be conducted by a physician with experience of treating MPS as soon as possible after diagnosis.

This should include a full discussion regarding the disease pathology, progression, treatment options, and management. Ongoing information should be provided to optimise patient outcomes"

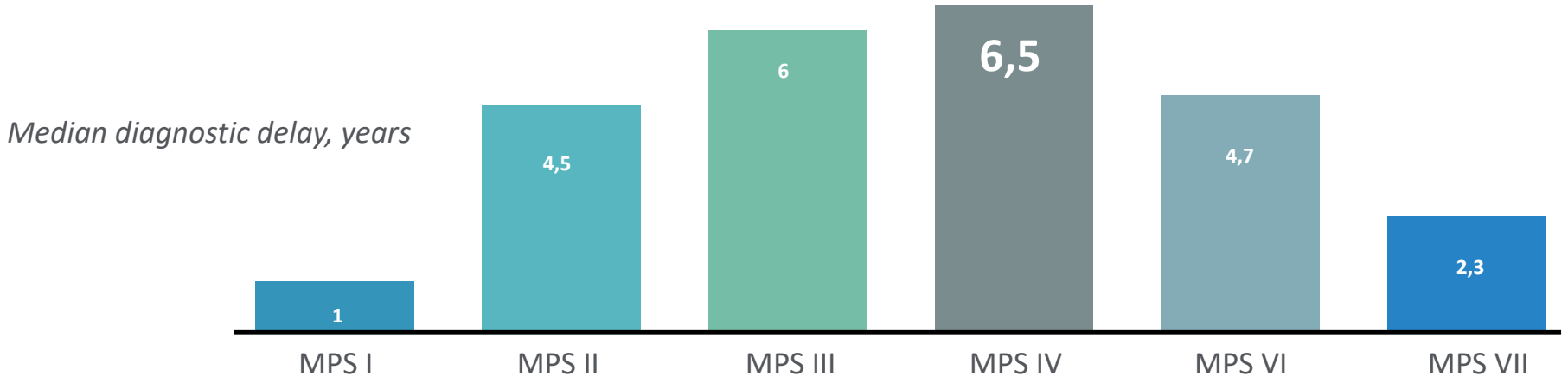
MPS, mucopolysaccharidosis

Akyol MU et al. *Orphanet J Rare Dis*. 2019;14:137

Delay to diagnosis across MPS types

Key findings

- Median delay to diagnosis was 2.9 years[1,a]
- In 20% of cases, delays ≥10 years were observed[2,a]
- 41% of the physicians surveyed were unaware of the association between some signs and symptoms and MPS[3,b]



[a]Findings from the systematic literature review; [b]Findings from the physician survey.

1. Mubarack F et al. Presented at the 13th International Congress of Inborn Errors of Metabolism: September 5–8, 2017, Rio de Janeiro, Brazil, 662;
2. Clarke L. et al. *JIEMS.* 2018;7:1–12.; 3. Clarke L et al. Presented at the 13th International Congress of Inborn Errors of Metabolism: September 5–8, 2017, Rio de Janeiro, Brazil, 649.

Recommendations cover five key areas of patient management

General principles for the management of MPS IVA and VI

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ENT, ear, nose, and throat; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplantation; MPS, mucopolysaccharidosis.

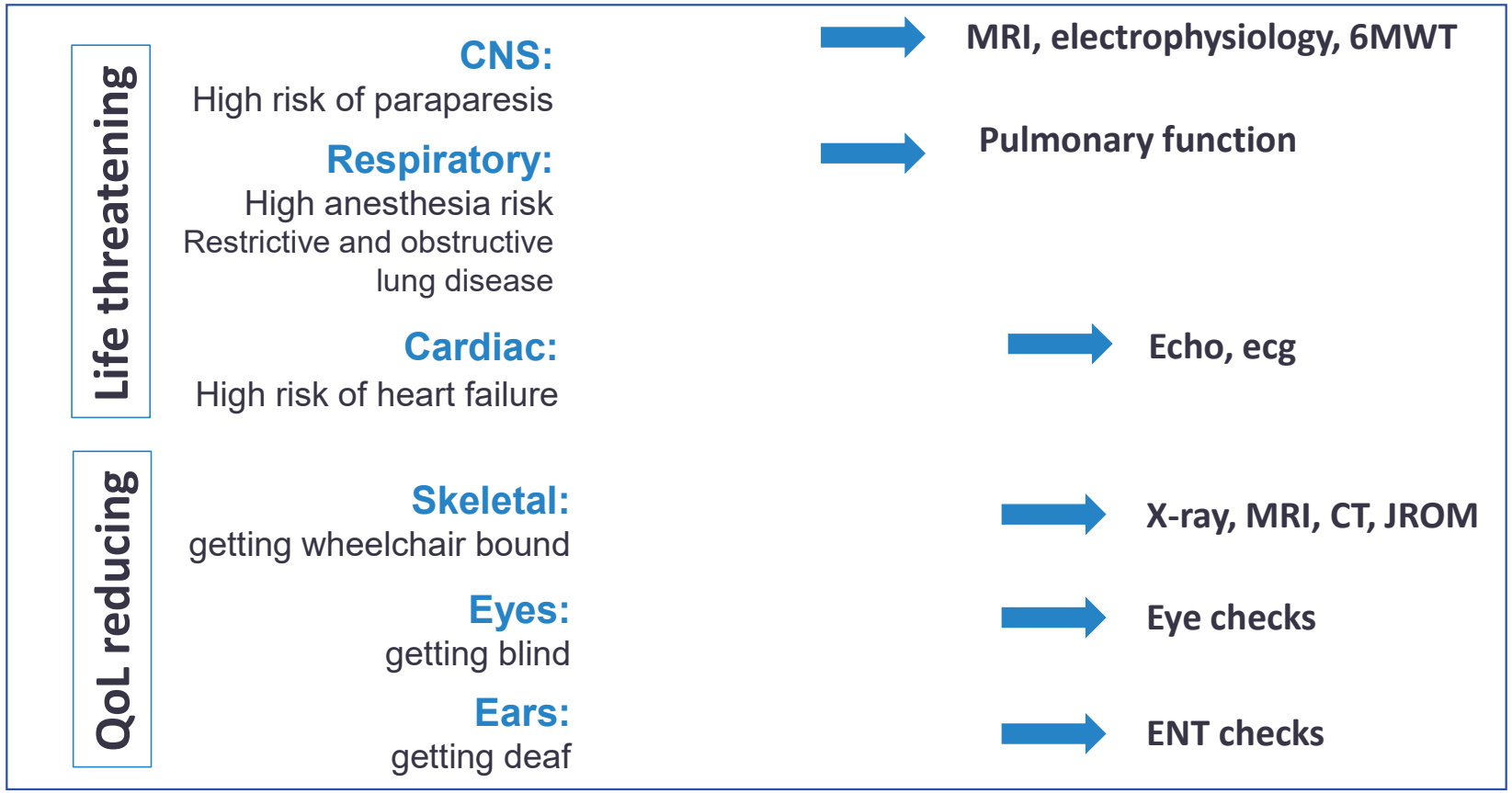
Akyol MU et al. Orphanet J Rare Dis.2019;14:118; Akyol MU et al. *Orphanet J Rare Dis*. 2019;14:137.

Care by a MDT is critical to manage the multisystem manifestations of MPSIVA and MPS VI

The MDT should ideally including **metabolic specialists, surgeons, and allied healthcare professionals** (including, but not limited to, nurses, physiotherapists, occupational therapists, psychologists, speech pathologists and audiologists, as medically appropriate), who must all work together to manage the diverse range of disease manifestations of MPS IVA/MPSVI

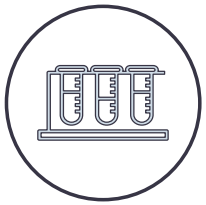
Akyol MU et al. *Orphanet J Rare Dis*. 2019;14:118

MPSs –checking all affected organ systems



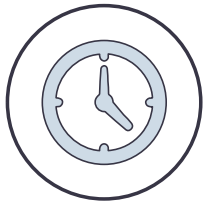
1. Presenter's own picture with permission of the patient, Wraith JE, Clarke JTR. In: *Physician's Guide to the Treatment and Follow-up of Metabolic Diseases*. 2006:195–203.
2. Scarpa et al. Orphanet Journal of Rare Diseases 2011, 6:72

Baseline and ongoing assessments are critical to monitor disease progression and treatment effect



"A **comprehensive medical history** and **multi-system evaluation** should be conducted **within days of diagnosis** to set a baseline for ongoing assessments and evaluate the physical and neurological manifestations of disease, functional ability, and **disease burden**"

"**Ongoing and regular, multi-system monitoring** and assessments are recommended to track the natural history of MPS IVA/MPS VI, monitor the impact of treatment, and assess the need for treatment interventions to manage the symptoms of MPS IVA and MPS VI"



"Timely interventions are recommended where clinically indicated by monitoring, to help **avoid irreversible damage** caused by the **natural history of MPS IVA/MPS VI**, and to **manage the disease manifestations** and maintain **long-term QoL"**

MPS, mucopolysaccharidosis; QoL, quality of life Akyol MU et al. *Orphanet J Rare Dis*. 2019;14:118

For optimal care: baseline assessments and follow up

Assessments should include:

- Endurance testing (e.g. 6MWT)[†]
- Growth, including height and weight
- Total urinary GAG levels
- Respiratory function (if age-appropriate)
- Pain severity
- ADL (e.g. MPS-HAQ)
- QoL (e.g. EQ-5D-5L)
- Evaluation of upper and lower limb function
- Evaluation for possible cervical cord compression

Both baseline (prior to ERT initiation) and regular follow-up assessments are critical to measuring ERT efficacy and setting treatment expectations with each individual patient

[†]Adaptations such as a 25-foot walk test can be used for patients with limited mobility.6MWT, 6-minute walk test; ADL, activities of daily living; EQ-5D-5L, 5-level EQ-5D; ERT, enzyme replacement therapy; GAG, glycosaminoglycan; HAQ, health-assessment questionnaire; MPS, mucopolysaccharidosis; QoL, quality of life. Akyol MU et al. Orphanet J Rare Dis.2019;14:118; Akyol MU et al. *Orphanet J Rare Dis*. 2019;14:137.

Multi-system assessments should be conducted at diagnosis and regularly thereafter (1 of 2)

ASSESSMENT	AT DIAGNOSIS	AT EVERY CLINIC VISIT	EVERY 6 MONTHS	EVERY 12 MONTHS	EVERY 24–36 MONTHS
Physical examination[a]		✓			
RADIOLOGY					
AP pelvis radiograph	✓				
Standing or sitting plain radiography of cervical and thoracolumbar spine	✓				✓ (or sooner[b])
MRI: whole spine[c]	✓			✓	
MRI: brain	✓				
ENDURANCE					
6-minute walk test[d]	✓			✓	
GROWTH					
Assessment of growth Should include measurement of height, weight, head circumference (≤3 years), and Tanner pubertal stage (until maturity)	✓	✓			
NEUROLOGY					
Neurological exam	✓	✓			
MPS VI: Clinical examination to evaluate CTS	✓		✓		

Akyol MU, Orphanet J Rare Dis. 2019 May 29;14(1) Orphanet J Rare Dis. 2019 Jun 13;14(1):137 .

Multi-system assessments should be conducted at diagnosis and regularly thereafter (2 of 2)

ASSESSMENT	AT DIAGNOSIS	AT EVERY CLINIC VISIT	EVERY 6 MONTHS	EVERY 12 MONTHS	EVERY 24–36 MONTHS
CARDIOLOGY					
Cardiac evaluation[e]	✓			✓	
RESPIRATORY FUNCTION/SLEEP DISORDERS					
Spirometry[f]	✓			✓ (in children)	✓ (in adults)
Overnight sleep study	✓				✓
ENT					
ENT evaluation[g]	✓		✓ (in children)	✓ (in adults)	
Audiometric assessment	✓			✓	
OPHTHALMOLOGY					
Comprehensive ophthalmologic assessment[h]	✓		✓		
ORAL HEALTH					
Monitoring of dental development	✓			✓	
DISEASE BURDEN					
Assessment of PROs using questionnaires (EQ-5D-5L and MPS HAQ)	✓			✓	

Akyol MU, Orphanet J Rare Dis. 2019 May 29;14(1).

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Akyol MU et al. Orphanet J Rare Dis.2019;14:118; Akyol MU et al. *Orphanet J Rare Dis*. 2019;14:137.

Specific anaesthesiological challenges in MPS

Difficult positioning
Deformity of the chest cage
Enlarged abdomen
Contractures

Limited co-operation
Intellectual disability

Postoperative:
Intensive care
Weaning
Airway swelling

higher peri-operative mortality
a specialized center is needed

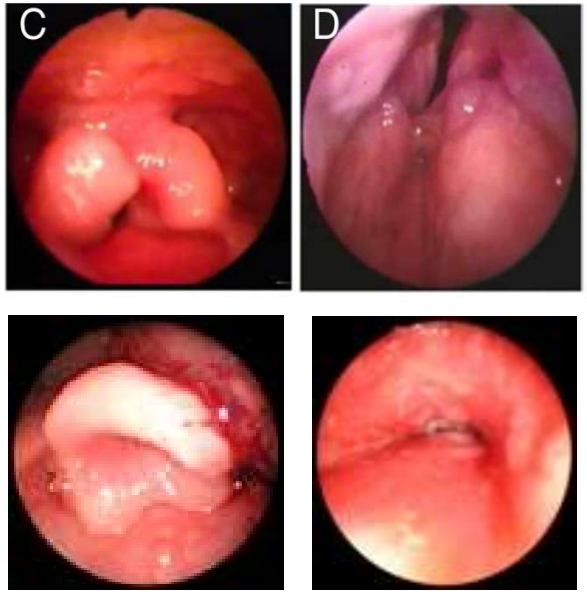
Difficult airways
Dwarfism, short neck
Large head, hypertelorism
Thickened and less flexible epiglottis, narrowed airways, macroglossia
Cervical spine flexibility
Atlanto-axial instability

Limited cardio-respiratory resources
Haemodynamically significant heart changes, cardiomyopathy
Recurrent airway infections
Restrictive and obstructive lung disease

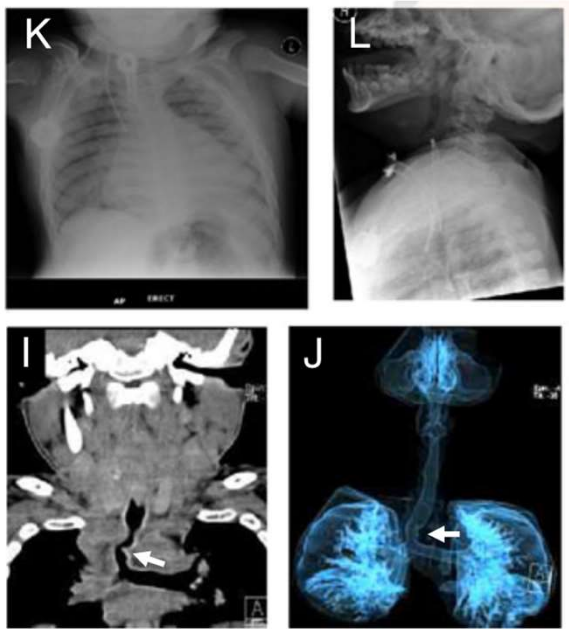
King et al. *Anaesthesia* 1984;39(2):126–31.

Reasons for high anesthesia risk

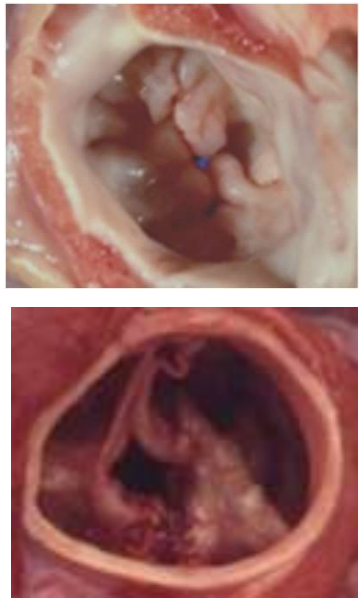
Narrowed upper airways



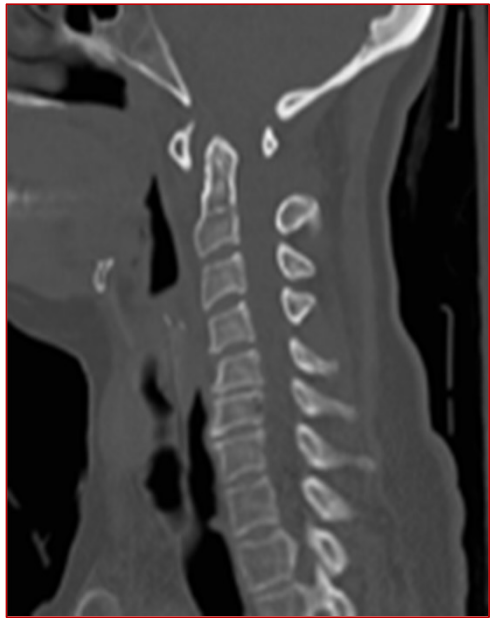
Restrictive and obstructive lung disease



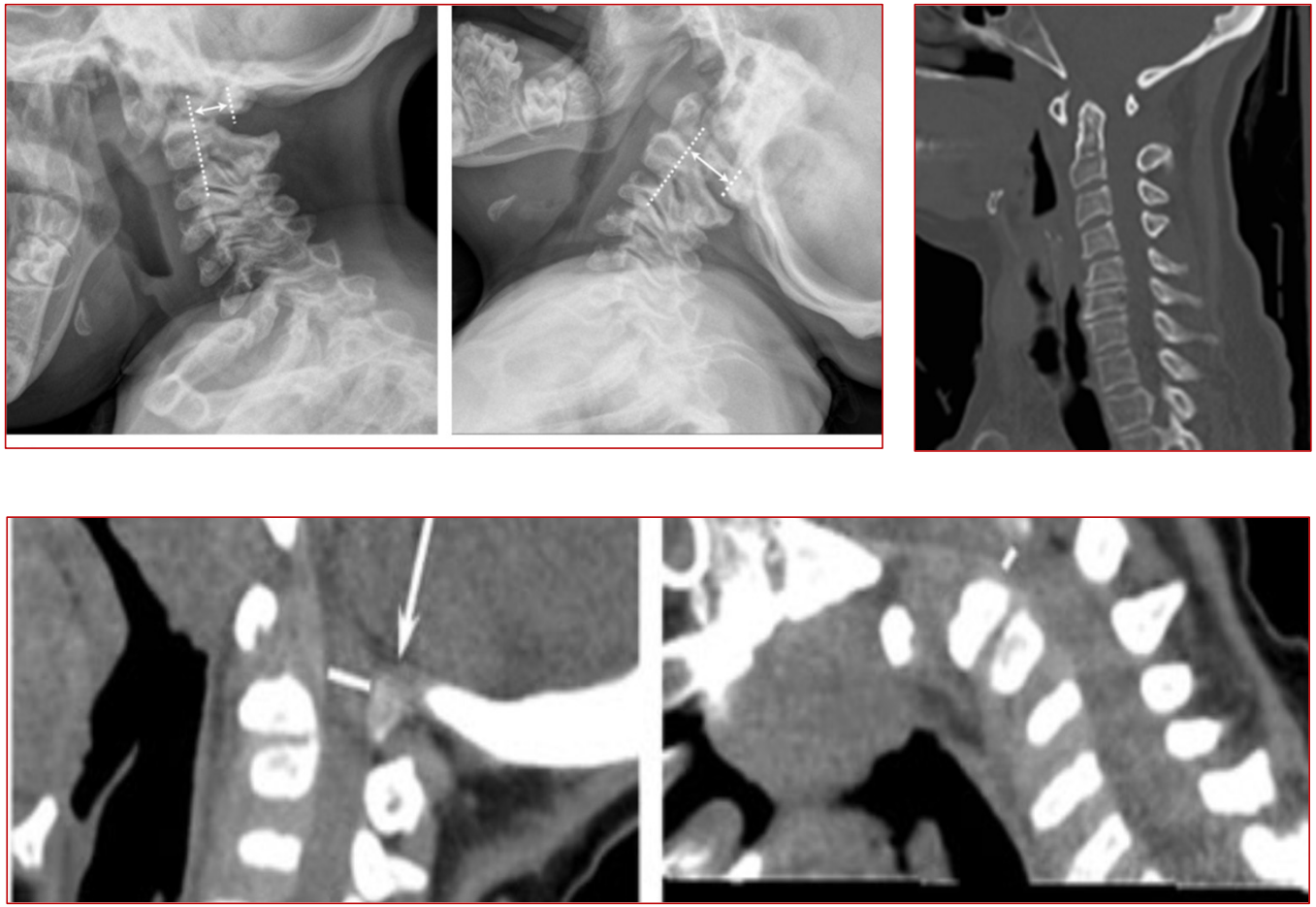
Heart valve stenosis/ insufficiency



Atlantoaxial instability



Atlano-axial instability, mainly in MPS IVA



Adapted from Solanki GA, et al. Mol Genet Metab. 2016 Aug;118(4):310-8

Preoperative evaluation and planning

- **Cardiopulmonary status**
  Cardiological complications are the main cause of intraoperative death
  → **1. Echo and ECG**
  2. Pulmonary testing

- **Conditions to intubate**
  Ventilation with a mask possible?
  Size of the equipment?
  Atlanto-axial instability?
  → **3. Laryngoscopy**

- **Conditions to ventilate**
  Tracheal stenosis or malacia
  Intraoperative positioning
  → **4. MRI cervical spine**
  5. CT scan airways

- **Conditions to extubate**
  Early extubation inside the operating theater, tracheotomy stand by, intensive care, emergency management:
  → **6. Organizing management and team!**

Akyol MU et al. Orphanet J Rare Dis. 2019;14:118

Due to greater surgical risk, specific actions are required prior to anesthesia and surgery

Multidisciplinary team

- **An anesthetist with experience in treating MPS patients should** supervise pre-, peri-, and post-operative care
- **Access to intensive care unit** and support by an experienced team capable of performing tracheotomy if required

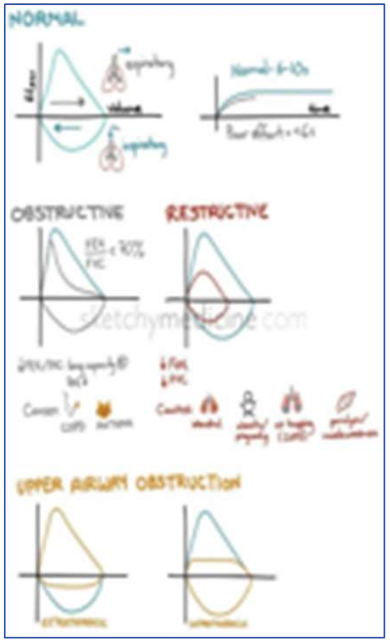
Surgery

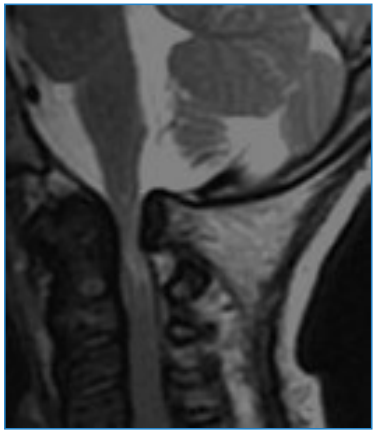
- extreme caution to avoid general anesthesia in a high-risk situation or during pregnancy
- ENT, respiratory, cardiac, and radiological assessments required prior to anesthesia
- Maintaining a **neutral neck position is critical** to avoid paralysis
  - Use of techniques strongly recommended e.g. LMA, intubation with video laryngoscope, or fiberoptic intubation

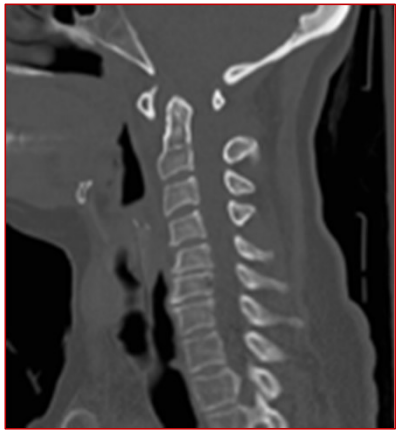
Akyol MU et al. Orphanet J Rare Dis. 2019;14:118

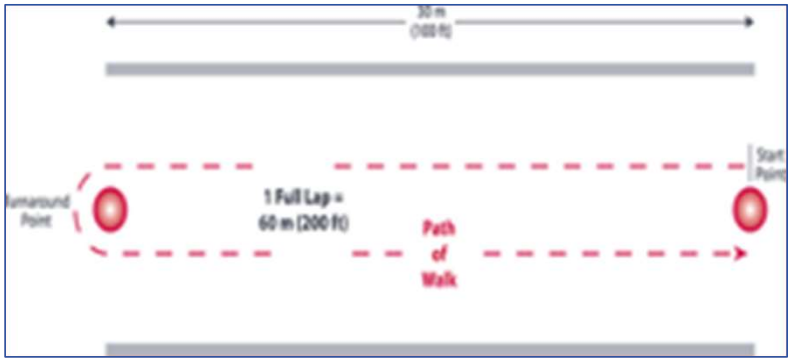
Life threatening disease complication in MPS I, (II), IVA and VI: craniocervical cord compression

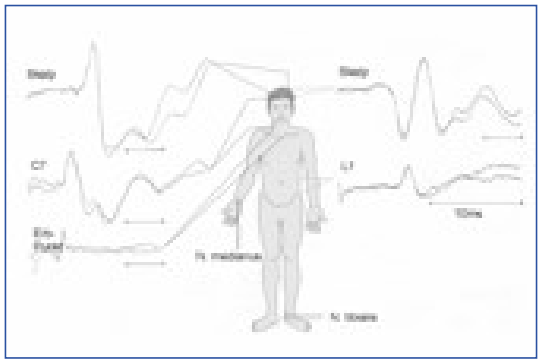
- Neurological exam
- MRI (flex/ex)
- Pulmonary function
- 6 Minute Walk Test
- 3D-CT
- SEP
- CSF flow studies
- Polysomnography





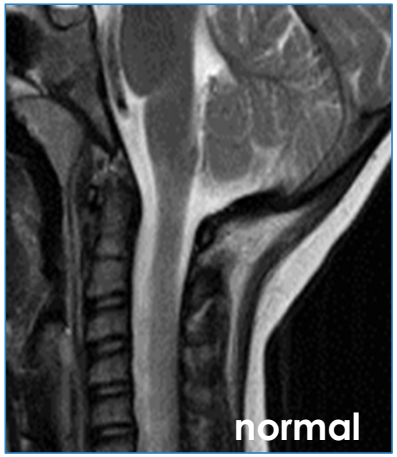


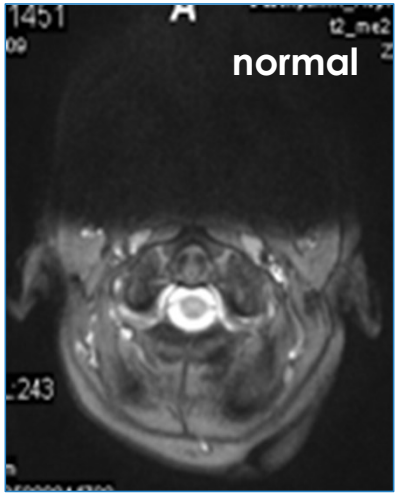


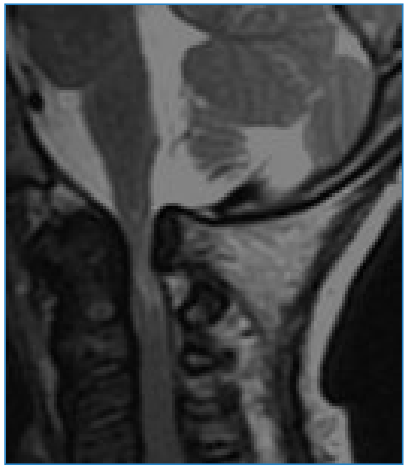


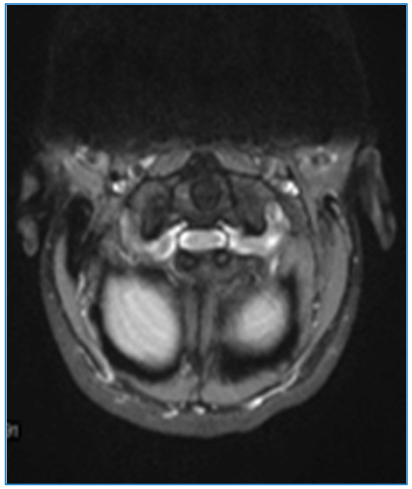
Own summary due to literature
https://sketchymedicine.com/2011/10/pulmonary-function-test-patterns/Kaur, Jaspreet & Malik, Manoj & Sharma, Parul & Sangwan, Sumedha & S, Kulandaivelan. (2017). Prevalence and Fitness of Diabetics in Hisar, Haryana, India. Romanian journal of diabetes, nutrition and metabolic diseases. 24. 10.1515/rjdnmd-2017-0015.

Results after decompression surgery (MPS VI)

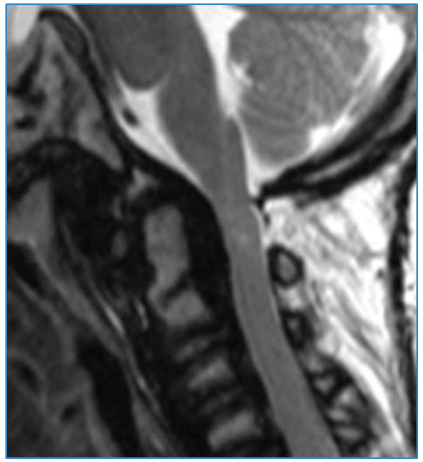


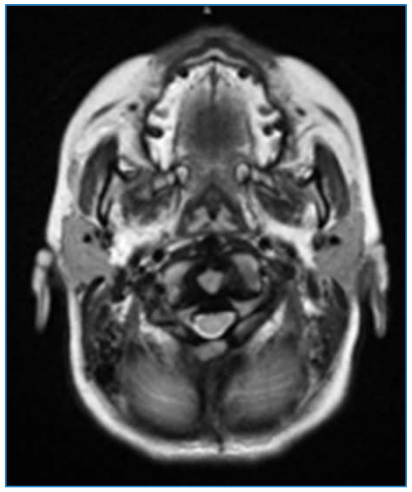




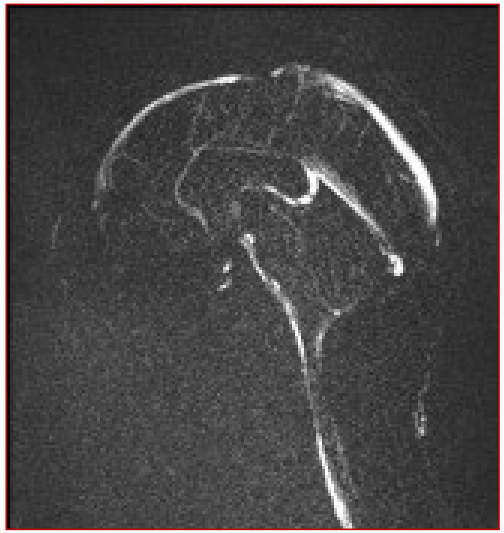


Preoperative MRI





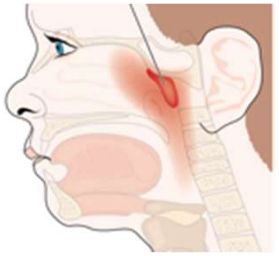
Postoperative MRI

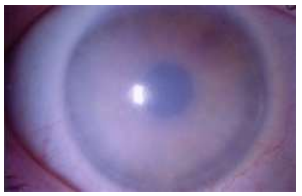


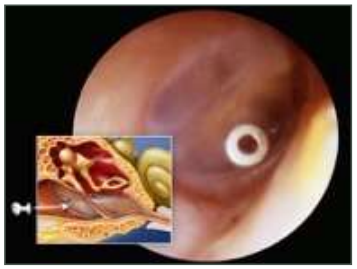
Presenter's own picture with permission of the patient

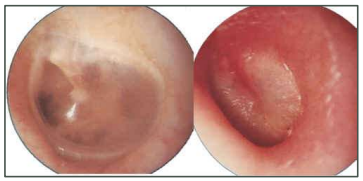
Quality of life reducing disease complications: craniofacial, ENT, eye and teeth

- Coarse facial features (prominent brow, broad nose, full lips, large jowls)
- Macroglossia
- Deafness — hearing aids
- Recurrent ear infections — ventilation tubes, antibiotics
- Chronic rhinorrhoea — Inhalation
- Adenoids, hypertrophic tonsils — adenoidectomy, tonsillotomie
- Visual impairment — glasses
- Corneal clouding — corneal transplantation
- Glaucoma (MPS VI) — medication, surgery
- Dental enamel defects — regular care and check up









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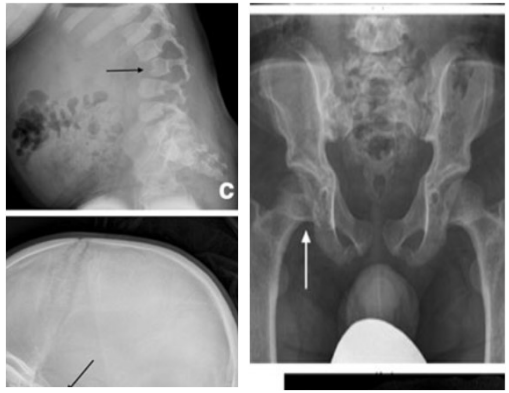
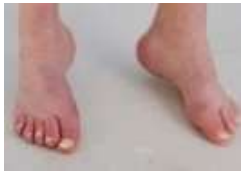
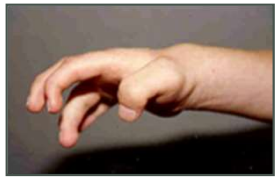
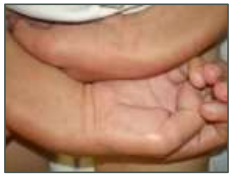
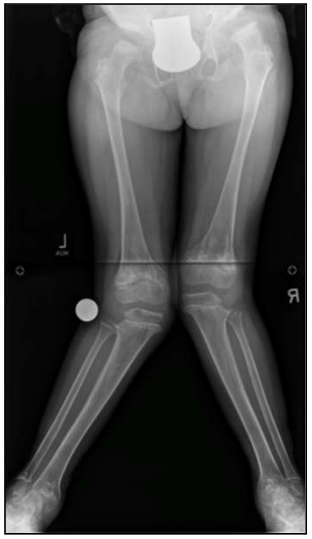
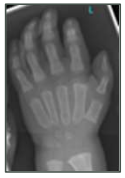
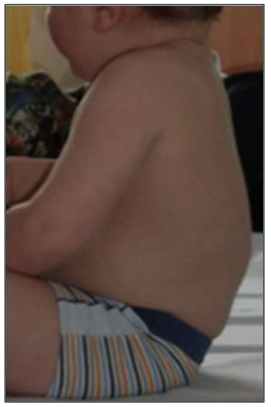
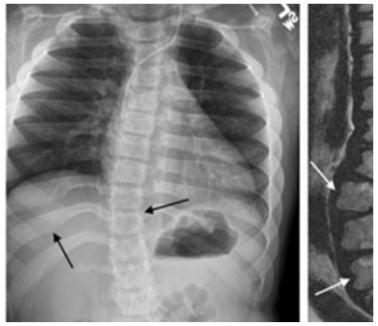
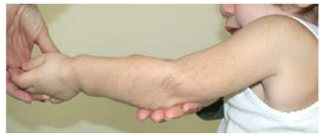
https://earsurgeon.in/conditions/best-adenoids-doctor-in-hyderabad/

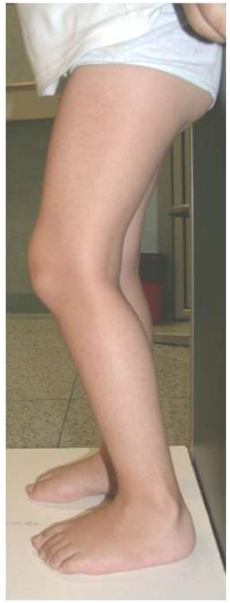
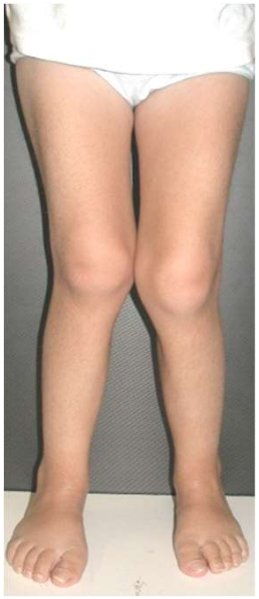
Quality of life reducing disease complications: skeleton and joints

- Joint stiffness and contractures, pain — physiotherapy, orthosis
- knock knees — hemiepiphysiodesis, orthosis
- Hip dysplasia — physiotherapy, osteotomy, hip replacement
- Thorakolumbar kysphskoliosis — corsets, decompression surgery, stabilization
- **MPS I, II, VI:** Carpal tunnel syndrome — decompression surgery
- Above average growth until age 3, then slowing of growth

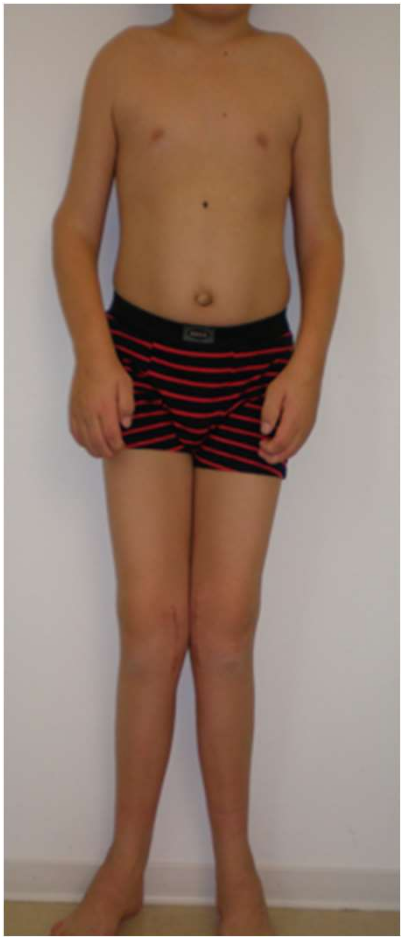



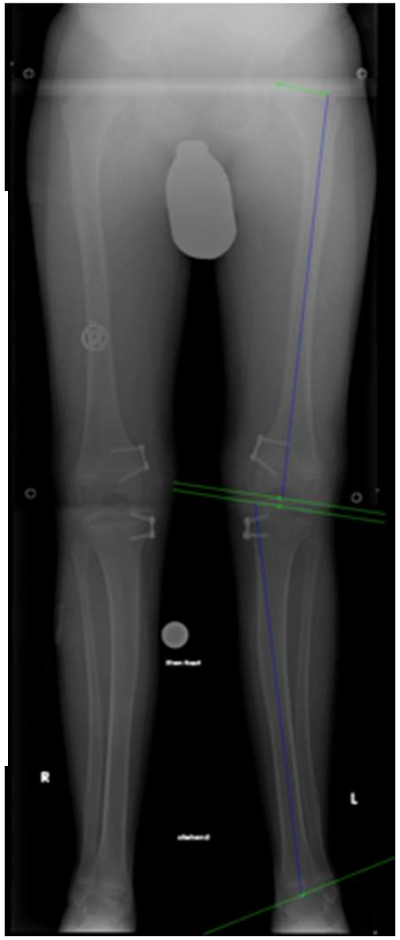
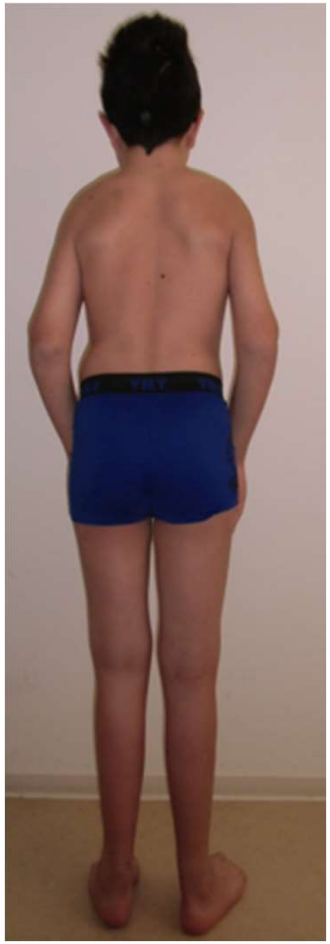
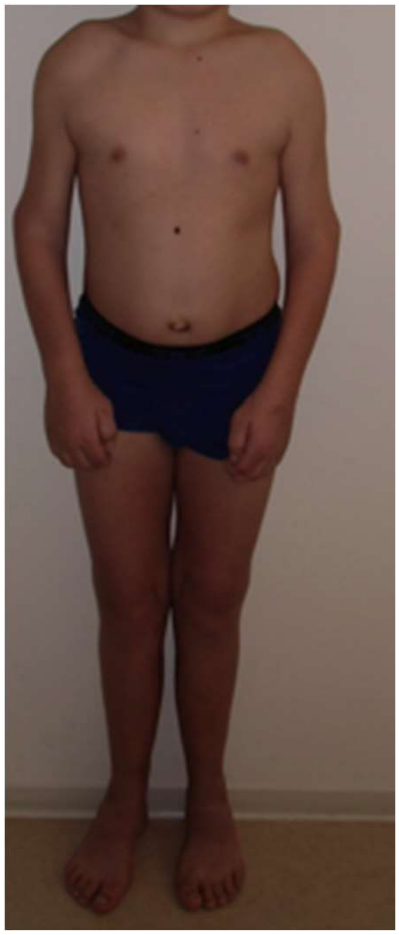




This slide was provided by Prof. Lampe, any needed necessary approvals before sharing this data have been secured by the speaker Burton BK, Giugliani R. Eur J Pediatr. 2012;171(4):631-639)

Quality of life reducing disease complication: operative treatment of genua valga: hemiepiphysiodesis



12 yrs., MPSII – prior surgery

1 years after surgery

Patients with limb and spinal manifestations may have the option for surgical intervention

Clinical manifestation	
	Limb surgeries
Hip pain, reduced walking, and endurance related to hip disease, as well as abnormal radiographic findings	Hip reconstruction is not routinely indicated but may be considered in pediatric MPS VI/MPS IVA patients Hip replacement can be considered in adult patients
Genu valgum	Growth modulation is recommended as early as possible during the period of growth
	Spinal surgeries
Evidence of spinal cord compression[†]	Decompression of the spinal cord is recommended
Spinal instability	Spinal stabilization of the craniocervical junction with either cervical fusion or occipital-cervical fusion is recommended
Progressive radiographic changes, intractable pain, and clinical deterioration as defined by gait, lung function, and changes in the degree of kyphosis	Correction of thoracolumbar kyphoscoliosis is recommended

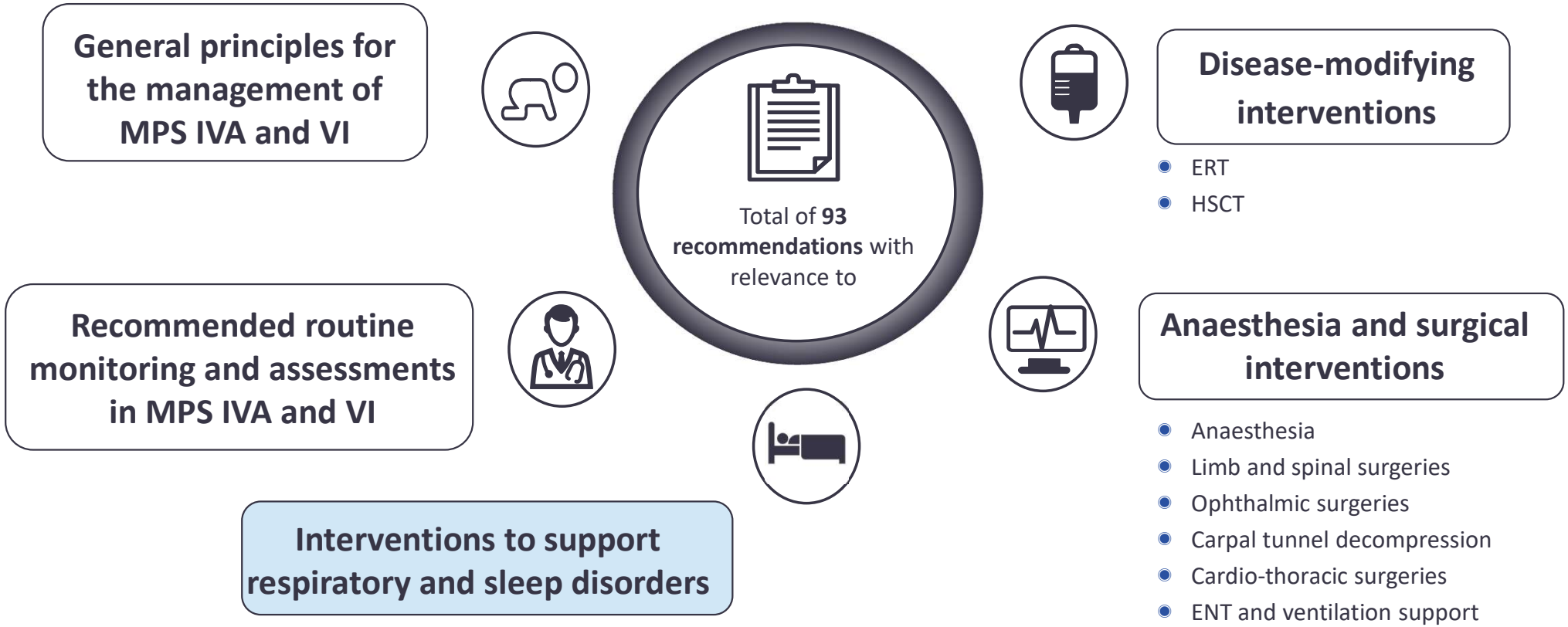
Akyol MU et al. *Orphanet J Rare Dis*. 2019;14:118

Surgical intervention may also be considered for manifestations of the hand, eye, heart, and ENT

Surgery	Recommendation
Carpal tunnel decompression (MPSVI)	New guidance address trigger finger in patients with MPS VI A1 and A3 pulley release is recommended in MPS VI patients who display obvious trigger finger
Ophthalmic surgery	Corneal transplantation can be considered for both MPS VI and IVA patients, with significant visual loss attributed to corneal opacification
Cardiac surgery	Cardiac (aortic, mitral) valve replacement should be considered in patients with MPS IV/MPS VI who display symptomatic and severe valve stenosis or regurgitation
ENT surgery	Following diagnosis, tonsillectomy and/or adenoidectomy is recommended for MPS VI/IVA patients who experience recurrent otitis media, snoring, and/or OSA without waiting for disease progression

Akyol MU et al. *Orphanet J Rare Dis*. 2019;14:118

Recommendations cover five key areas of patient management



ENT, ear, nose, and throat; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplantation; MPS, mucopolysaccharidosis.

Akyol MU et al. Orphanet J Rare Dis.2019;14:118; Akyol MU et al. *Orphanet J Rare Dis*. 2019;14:137.

Specific interventions are recommended to manage respiratory and sleep disorders

"CPAP therapy is recommended for patients with MPS VI/UVA who display the presence of OSA which persists after tonsillectomy and/or adenoidectomy"

"NIPPV therapy is recommended for patients with MPS VI/IVA who display nocturnal hypoventilation and are unresponsive to CPAP, or display daytime hypoventilation with increased $PaCO_2$ and/or serum HCO_3 levels"

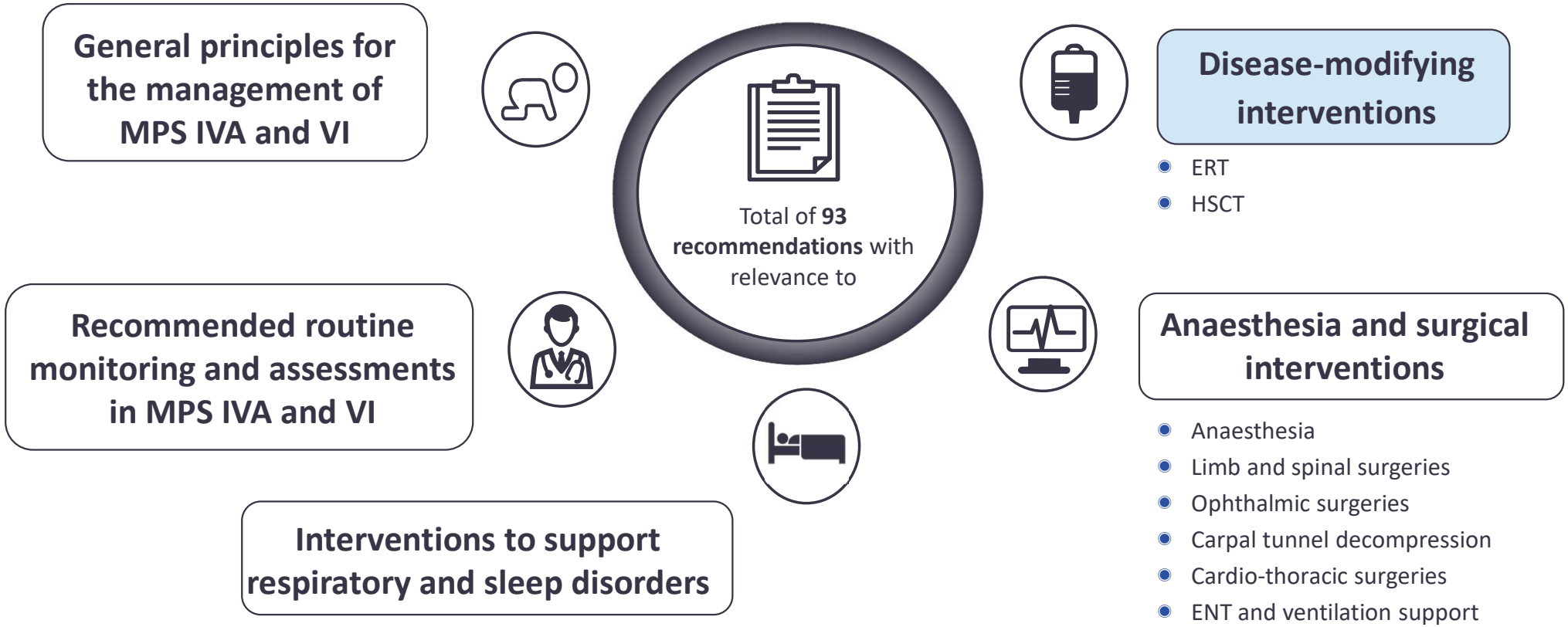
"Oxygen supplementation is recommended for patients with MPS VI/IVA who exhibit sleep apnea with nocturnal hypoxemia, and who do not tolerate CPAP or NIPPV masks"

"Patients with MPS VI/IVA should be monitored for development of hypercapnia after starting therapy with measurement of $PaCO_2$ and/or serum HCO_3 levels"

CPAP, continuous positive airway pressure; MPS, mucopolysaccharidosis; OSA, obstructive sleep apnea; NIPPV, non-invasive positive pressure ventilation

Akyol MU et al. *Orphanet J Rare Dis.* 2019;14:118

Recommendations cover five key areas of patient management



ENT, ear, nose, and throat; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplantation; MPS, mucopolysaccharidosis.

Akyol MU et al. Orphanet J Rare Dis.2019;14:118; Akyol MU et al. *Orphanet J Rare Dis*. 2019;14:137.

Treatment with enzyme replacement therapy should be started promptly after diagnosis and maintained long-term

Galsulfase in MPS VI

"Initiation of **long-term ERT** with galsulfase at a dose of 1 mg/kg/week by intravenous infusion is recommended in patients with MPS VI **as soon as possible after a confirmed diagnosis"**

"Galsulfase has been shown to improve endurance…and pulmonary function…which may, in part, be attributed to growth in young patients"

Elosulfase alfa in MPS IV A

"Initiation of **long-term ERT** with elosulfase alfa at a dose of 2 mg/kg/week through intravenous infusion is recommended in all patients with MPS IVA as **soon as possible after a confirmed diagnosis"**

"The **early initiation of ERT** will likely **change the course of disease** in patients with MPS IVA;

additional studies needed to determine the long-term outcomes of patients

ERT, enzyme replacement therapy; MPS, mucopolysaccharidosis, Akyol MU et al. *Orphanet J Rare Dis*. 2019;14:118

Elosulfase alfa for MPS IVA and Galsulfase for MPS VI are currently the only licensed disease-specific treatments

Galsulfase in MPS VI

- The benefits of ERT initiation at an early age are well-demonstrated in multiple sibling-controlled studies of patients with MPS VI
- If initiated early, galsulfase may result **in improvement in growth velocity,** and may **prevent the progression of cardiac valve abnormalities;** comparative studies of patients who have not received ERT will be critical to further establish treatment effect
- Early initiation of long-term treatment with galsulfase is associated with a **trend for improvement in spleen and liver size, facial dysmorphia, joint mobility and decreased pain**; findings also suggest galsulfase **may slow bone disease progression**
- **HSCT may be an option**; it is important to consider the associated risks of morbidity and mortality and the procedure should only be performed by a MDT that is experienced with caring for MPS VI patients

Elosulfase alfa in MPS IV A

- elosulfase alfa has been shown to **improve endurance and exercise capacity**, and in some patients, **reduce pain**
- Long-term treatment with elosulfase alfa is associated with partial **recovery of functional abilities**, and **improvement in performance of ADL**
- Early intervention with elosulfase alfa is associated with a **trend towards improvement in growth**. Additional studies will be critical to determining comprehensive long-term outcomes of patients who initiated ERT at an early age
- **HSCT is not recommended** for patients with MPS IVA

ADL, activities of daily living; ERT, enzyme replacement therapy; HSCT, hematopoietic stem cell transplantation

Genotype-Phenotype correlation in MPS I

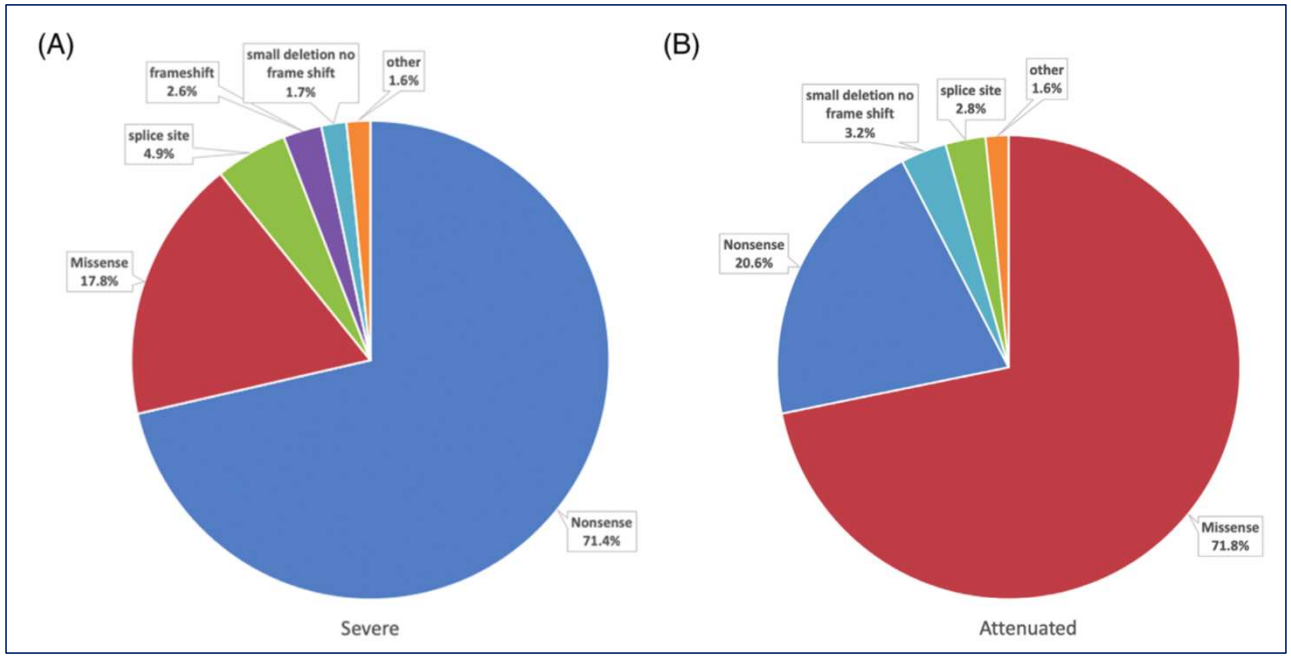


TABLE 3 Severe MPS I patients: N = 380

Two severe[a] variants 257 (67.6%)	Recurrent genotypes[b] 296 (77.9%)		Unique genotype[c] 47 (12.4%)
	W402X/W402X	109 (28.7%)	
	W402X/Q70X	61 (16.1%)	
	Q70X/Q70X	24 (6.3%)	
	R628X/R628X	6 (1.6%)	
	p.S16_A19del/W402X	6 (1.6%)	
	R619X/W402X	5 (1.3%)	

TABLE 4 Attenuated MPS I patients: N=158

Missense variants[a] 154 (95.4%)	Recurrent genotype[b] 95 (60%)		Unique genotype[c] 63 (40%)
	L490P/L490P	21 (13.3%)	
	P533R/P533R	17 (10.8%)	
	P533R/W402X	3 (1.9%)	
	P533R/Q70X	2 (1.3%)	
	L238Q/W402X	6 (3.8%)	
	L238Q/Q70X	2 (1.3%)	

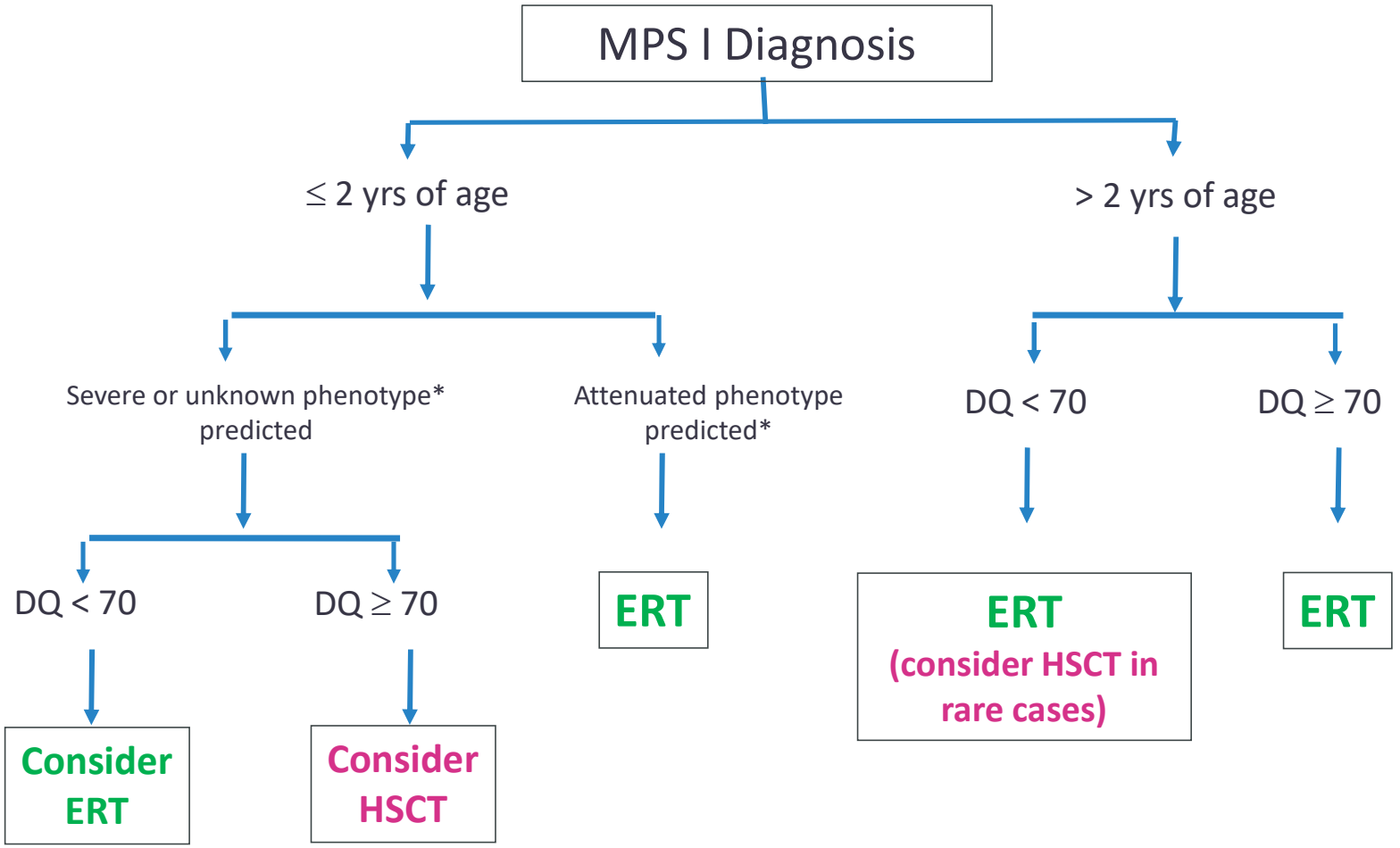
n= 556 patients from the MPS I Registry

Severe phenotype n=380

Attenuated phenotype n=158

Clarke, Lorne A et al. “Genotype-phenotype relationships in mucopolysaccharidosis type I (MPS I): Insights from the International MPS I Registry.” *Clinical genetics* vol. 96,4 (2019): 281-289.

Recommendations for HSCT or ERT in MPS I



*Prediction of disease severity based on clinical picture, neurodevelopmental testing, genotype and other relevant information

Muenzer et al Pediatrics 2009, 123: 19-29

Management and treatment guidelines MPS I

	Initial Assessments	Every 6 mo	Every 12 mo	Every Other Year
General				
Demographic characteristics	X			
Patient diagnosis	X			
Medical history	X	X		
Physical examination	X	X		
General appearance	X	X		
Clinical assessments				
Neurologic/central nervous system				
Computed tomographic or MRI scans of brain	X			X
MRI scans of spine	X			X
Median nerve conduction velocity	X			X
Cognitive testing (DQ/IQ)	X		X	
Auditory				
Audiometry	X		X	
Ophthalmologic				
Visual acuity	X		X	
Retinal examination	X		X	
Corneal examination	X		X	
Respiratory				
Forced vital capacity/forced expiratory volume	X	X		
Sleep study	X		X	

	Initial Assessments	Every 6 mo	Every 12 mo	Every Other Year
Cardiac				
Echocardiography	X			X
Electrocardiography	X			X
Musculoskeletal				
Skeletal survey with radiographs[a]	X			X
Gastrointestinal				
Spleen volume[b]	X			X[c]
Liver volume[b]	X			X[c]
Vital signs and laboratory tests				
Height and weight	X	X		
Head circumference[a]	X	X		
Blood pressure	X	X		
Enzyme activity level	X			
Urinary glycosaminoglycan level	X	X[c]		
Urinalysis	X	X[c]		
Functional outcome measurements				
Mucopolysaccharidosis Health Assessment Questionnaire or other tools exploring functional ability and quality of life[d]	X		X	

Joseph Muenzer, et.a.l, **Mucopolysaccharidosis I: Management and Treatment Guidelines** *Pediatrics* 2009;123;19

Scarpa *et al. Orphanet Journal of Rare Diseases* 2011, **6**:72
http://www.ojrd.com/content/6/1/72

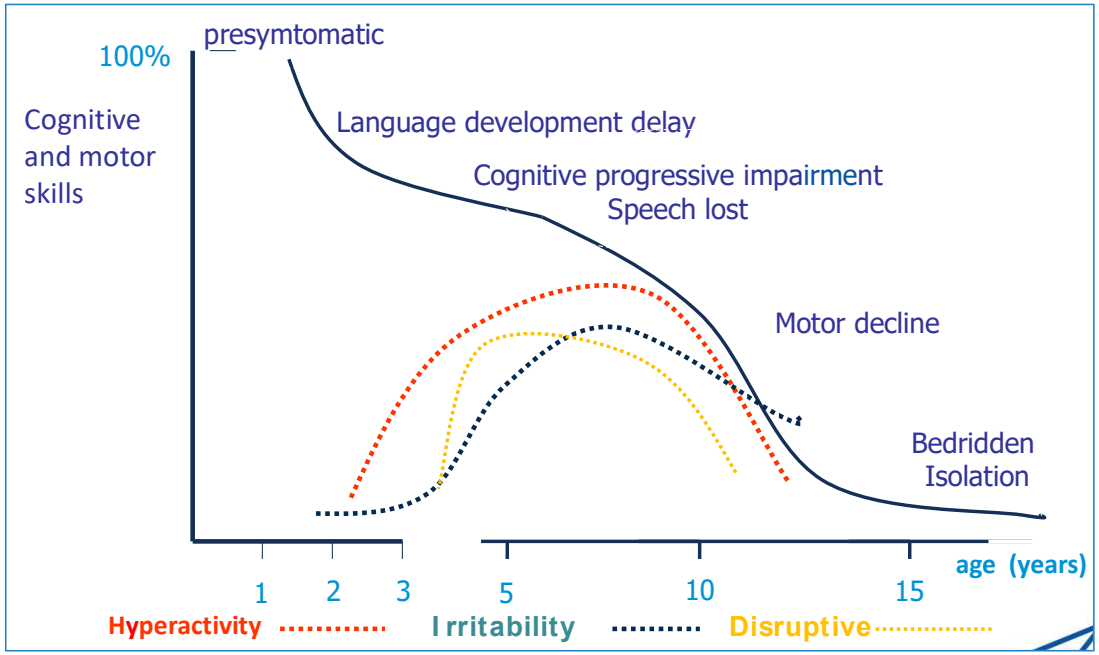
ORPHANET JOURNAL OF RARE DISEASES

REVIEW Open Access

Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease

What do we know about cognitive ability in MPS II?

- Approximately 2/3 of patients with MPS II will slow and then stop developing cognitive skills. They will then gradually lose the skills they have developed
- Some children begin to slow in ability at age 2 and others at age 5 and any time in between
  - This variability makes it difficult to predict the disease course
- Cognitive ability can be measured and can be accomplished for both clinical trials and patient management, but there are challenges[a]



Holt JB *et al. Pediatr* 2011;127:e1258–65; 2. Ziegler R and Shapiro E. *Cambridge University Press*; 2010:427–483.

Additional Assessments in MPS II (neuronopathic)

Nervous system	
Developmental delay	Medical history (achievement of developmental milestones),* neurobehavioral assessment/cognitive testing,* measurement of intelligence quotient†
Progressive mental impairment (cognitive dysfunction)	Neurobehavioral assessment/cognitive testing,* measurement of intelligence quotient†
Gait disturbance	Evaluation of sitting and standing posture and walking ability (6-minute walk test),* MRI of the brain and cranio-cervical junction†
Seizures	MRI of the brain and cranio-cervical junction*, electroencephalography†
Behavioural disturbances (over activity, obstinacy, aggression)	Neurobehavioral assessment/cognitive testing,* measurement of intelligence quotient†
Carpal tunnel syndrome	Electrophysiological testing of nerve conduction velocity†

Scarpa M, Almássy Z, Beck M, Bodamer O, Bruce IA, De Meirleir L, Guffon N, Guillén-Navarro E, Hensman P, Jones S, Kamin W, Kampmann C, Lampe C, Lavery CA, Teles EL, Link B, Lund AM, Malm G, Pitz S, Rothera M, Stewart C, Tylki-Szymańska A, van der Ploeg A, Walker R, Zeman J, Wraith JE; Hunter Syndrome Europena Expert Council. Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease. Orphanet J Rare Dis. 2011 Nov 7;6:72.

Sanfilippo syndrome: consensus guidelines for clinical care

- 64 clinicians representing 21 specialty areas (from 14 countries)
  - 59% (n=38) had cared for ≥10 patients with Sanfilippo syndrome
  - 8% (n=18) had cared for >30 patients with Sanfilippo syndrome

- Consensus (defined as ≥75% responses of 'Strongly Agree' or 'Agree')
- 173 (94%) of 185 statements reached consensus

=> **178 final statements (>75% agreement)**

Diagnosis in Sanfilippo Syndrome

- **Early diagnosis of Sanfilippo syndrome is critical to ensure:**
  - optimal care for patients and their families by enabling access to specific supportive interventions to maximize peak abilities
  - slow rate of decline
  - improve quality of life
  - accessing appropriate education and developmental therapies
  - participate in clinical trials and/or receive treatments as they emerge
  - timely genetic counseling of affected families

- **Reasons for diagnostic delay (> 2 years)**
  - lack of disease awareness
  - the absence or subtle presentation of somatic symptoms
  - neurological symptoms that can be mistakenly considered as idiopathic developmental delays and behavioral challenges

Differential diagnosis:
- idiopathic developmental delay
- attention deficit
- hyperactivity disorder (ADHD)
- autism

Muschol N, Giugliani R, Jones SA, Muenzer J, Smith NJC, Whitley CB, Donnell M, Drake E, Elvidge K, Melton L, O'Neill C; MPS III Guideline Development Group. Sanfilippo syndrome: consensus guidelines for clinical care. Orphanet J Rare Dis. 2022 Oct 27;17(1):391.

Multidisciplinary approach in Sanfilippo syndrome

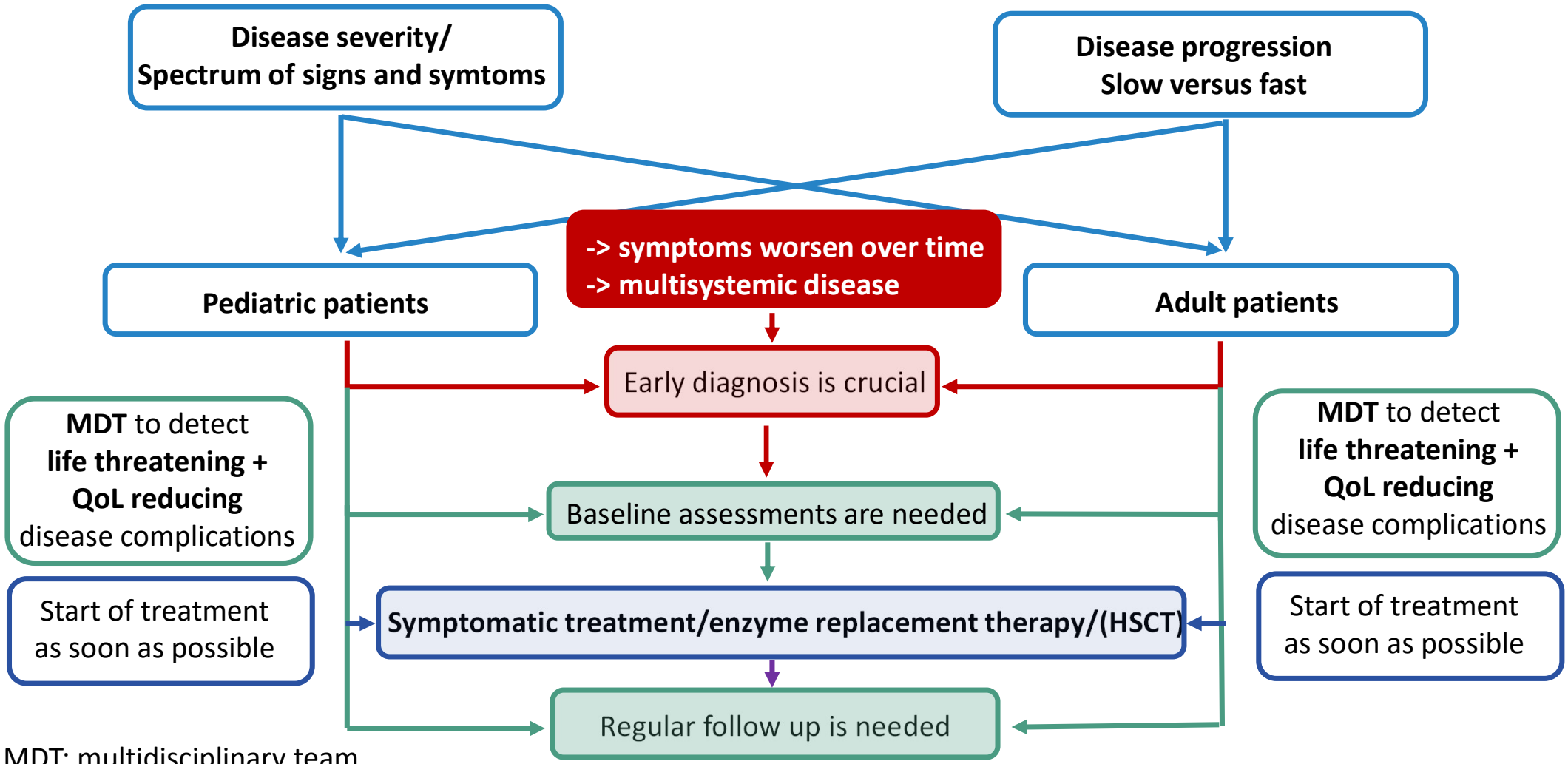
- Neurodevelopment/neurological
- Seizures
- Pain
- Hematology
- Occupational therapy
- Speech therapy
- Growth
- Puberty
- Family support

Area of assessment	At diagnosis	As clinically indicated
Neurodevelopment/ neurological	• Cognitive function (f • Adaptive behavior sk VABS) • Gross motor function • Fine motor skills • Tone • Sleep • Seizure activity • Movement (walking/ • Behavioral symptom • High-resolution MRI	al exam/history • High-resolution MRI (triggered by extreme behavioral changes, unexplained pain or distress, suspicion of headaches, suspicion of elevated intracranial pressure, sudden neurological or functional declines) • Evaluation for behavior-based therapy
Seizures		• EEG (triggered by suspected seizure activity; see the seizure management section)
ENT	• ENT examination • Audiologic testing	• ENT examination and audiologic testing; • Triggered by recurrent otitis media or suspected changes in hearing • At least 6-monthly if identified hearing loss or otitis media with effusion • Flexible endoscopy, prior to general anesthesia: • Triggered by suspicion of airway obstruction
Airway/respiratory	• Vital signs • Respiratory examinat	on with dilation months, or every ed • Sleep evaluation (triggered by sleep disturbance) • Medical workup (triggered by sleep disturbance, recurrent pneumonia, impaired secretion management) • Pre-operative assessment: anesthetic review, airway assessment, cardiology review, respiratory review, hematology review, neurologic review, palliative care, and nursing review
Ophthalmology	• Full ophthalmologic	• Full ophthalmologic evaluation (triggered by persistent unexplained pain, distress or agitation, falls) • Electroretinogram (triggered by suspicion of retinopathy) • Dental exam (triggered by persistent unexplained pain, distress or agitation)
Surgery		ng, and swallowing n tests • Monitor for gastroesophageal reflux (triggered by increased behavioral distress, sleep disturbance, and/or other clinical signs) • Diet assessment (triggered by weight loss or poor growth) • Abdominal imaging (triggered by persistent unexplained pain, distress or agitation)
Nutrition and gastroenterol	• Assessment of eating abilities • Electrolytes and liver	• Echocardiogram (at least 1-2 monthly if abnormalities on initial or subsequent assessments) • Holter monitoring (triggered by abnormal ECG)
Dental		
Cardiac	• Echocardiogram • ECG	

Key evaluations for patients in pain, distress, or with behavioral changes of undetermined etiology

Area of assessment	Evaluations
Neurodevelopment/ neurological	High-resolution MRI: assessing for causes of headaches, signs of raised intracranial pressure and/or other intermittent or acute abnormalities that could be a cause of pain, distress, or behavioral changes
ENT	ENT examination: assess for potential causes of unexplained pain, including infection
Ophthalmology	Full ophthalmologic evaluation: assess for potential causes of unexplained pain, distress, agitation, or falls
Dental	Dental exam: assess for potential causes of unexplained pain, distress, or agitation
Nutrition and gastroenterology	Assess for gastroesophageal reflux as potential cause of behavioral distress and/or sleep disturbance Abdominal imaging: assess for potential causes of unexplained pain, distress, or agitation
Orthopedic	Physical exam and X-rays: assess for potential causes of unexplained signs of discomfort or pain, particularly hip disease
Pain	Standardized pain assessments Caregiver proxy assessments
Laboratory investigations	Complete blood count, electrolytes, serum chemistries, and urine analysis
Detailed physical exam and history	Exam and history to include areas described above, as well as skin and genitourinary evaluation (including assessment for urinary retention)*

Summary MPS – disease with many variables



MDT: multidisciplinary team

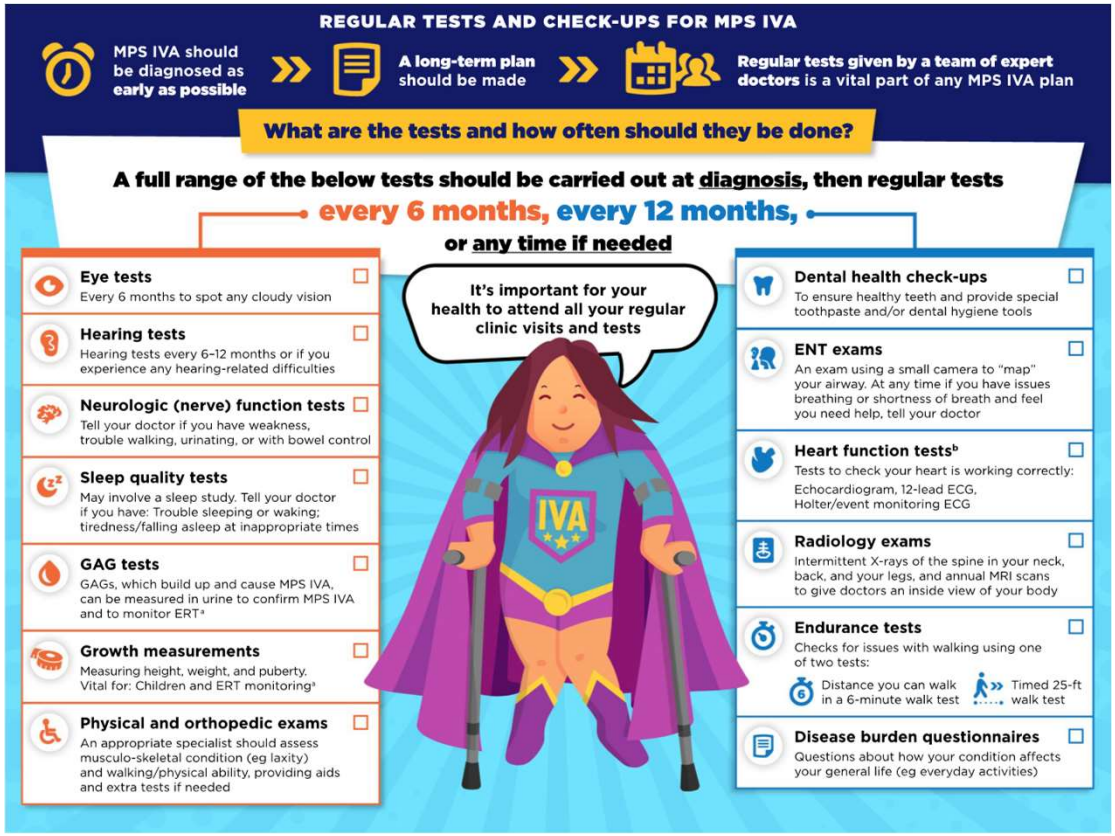
Patient-friendly medical communications: adaptation of the 2019 recommendations for the management of MPS VI and MPS IVA

Bruce IA et al. Addressing the need for patient-friendly medical communications: adaptation of the 2019 recommendations for the management of MPS VI and MPS IVA
Orphanet J Rare Dis. 2022 Mar 2;17(1):91.

Multidisciplinary team (MDT)

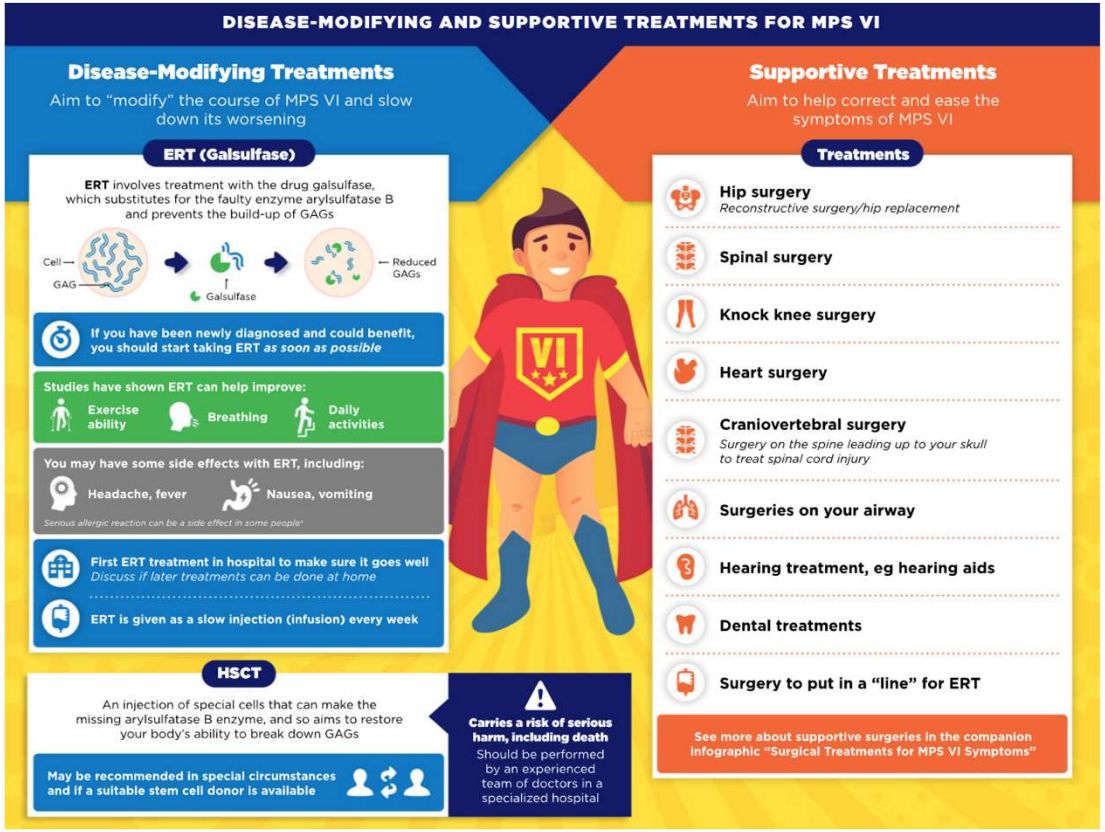
Bruce IA, Ezgü FS, Kampmann C, Kenis V, Mackenzie W, Stevens B, Walker R, Hendriksz C. Addressing the need for patient-friendly medical communications: adaptation of the 2019 recommendations for the management of MPS VI and MPS IVA. Orphanet J Rare Dis. 2022 Mar 2;17(1):91.

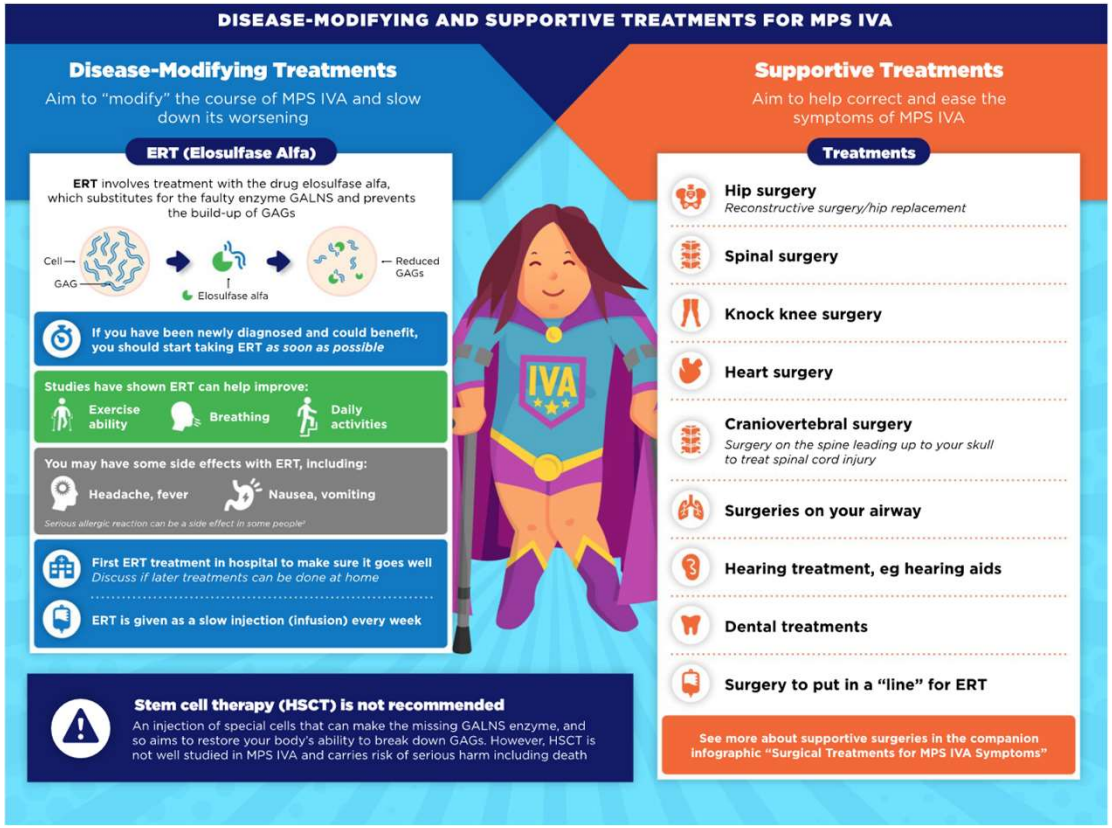
Regular tests and check ups



Bruce IA, Ezgü FS, Kampmann C, Kenis V, Mackenzie W, Stevens B, Walker R, Hendriksz C. Addressing the need for patient-friendly medical communications: adaptation of the 2019 recommendations for the management of MPS VI and MPS IVA. Orphanet J Rare Dis. 2022 Mar 2;17(1):91.

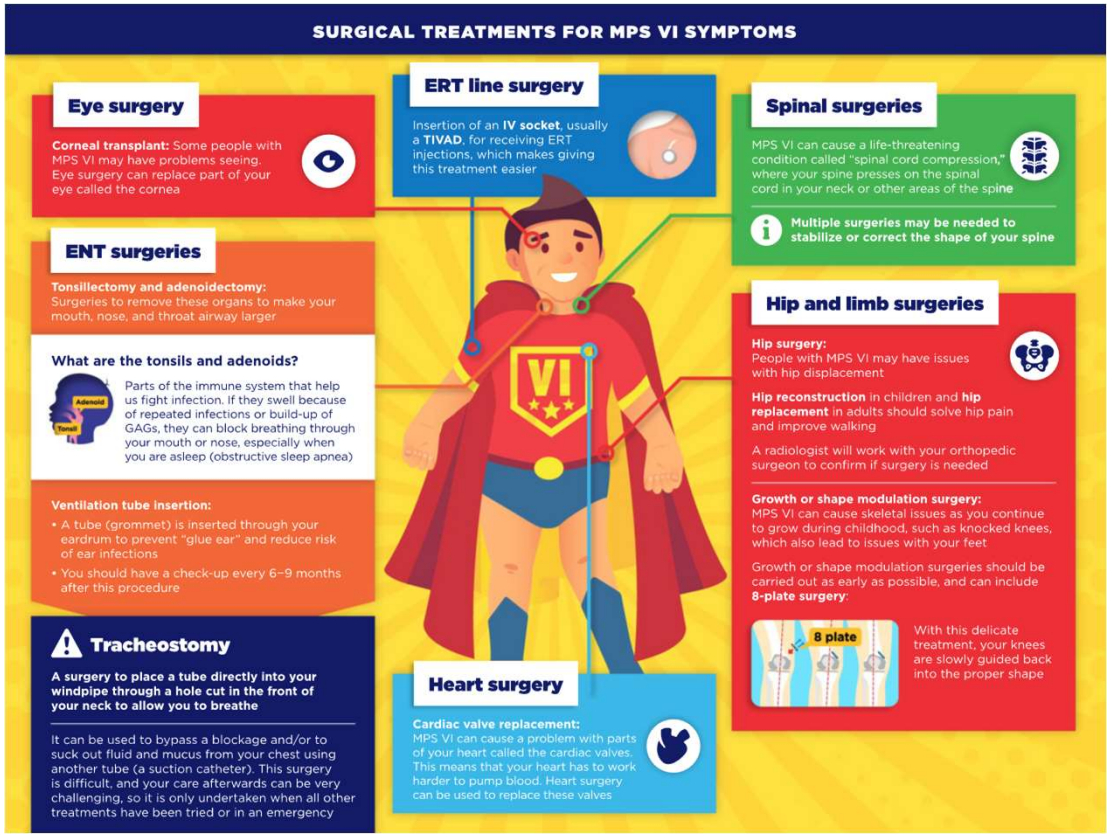
Disease modifying and supportive treatments

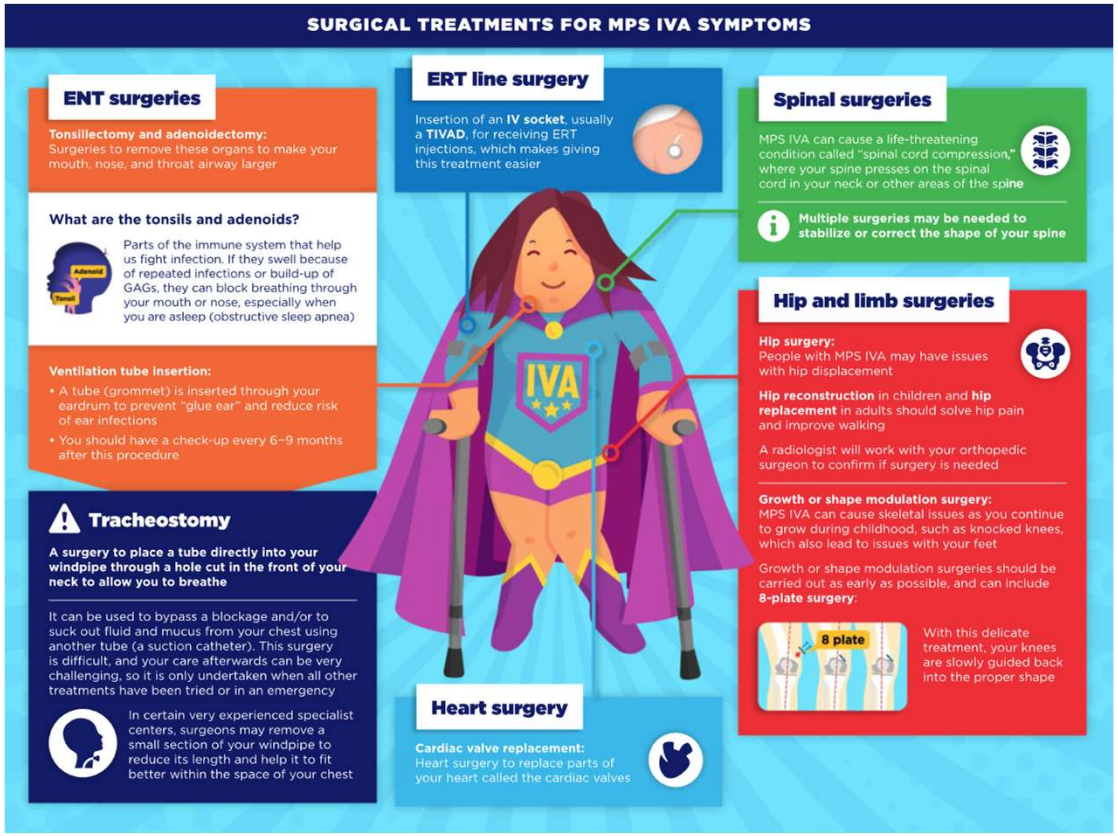




Bruce IA, Ezgü FS, Kampmann C, Kenis V, Mackenzie W, Stevens B, Walker R, Hendriksz C. Addressing the need for patient-friendly medical communications: adaptation of the 2019 recommendations for the management of MPS VI and MPS IVA. Orphanet J Rare Dis. 2022 Mar 2;17(1):91.

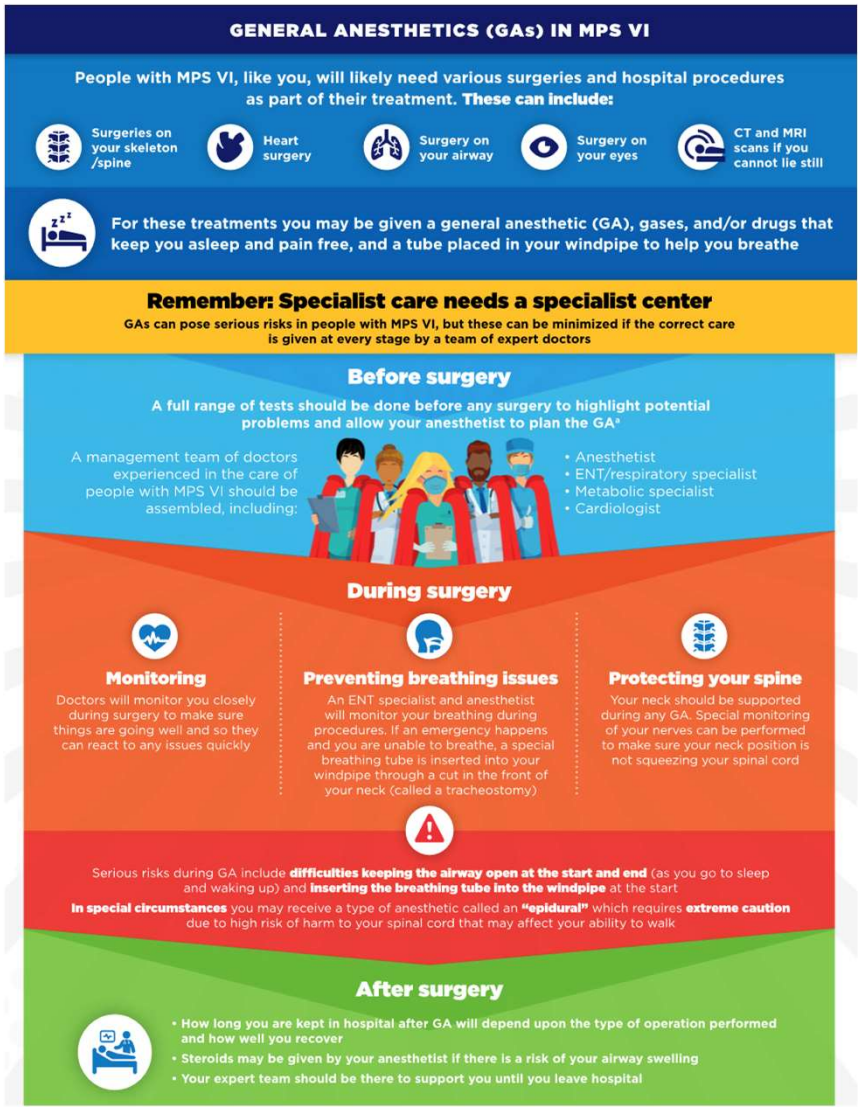
Surgical treatments for MPS VI/MPS IVA symptoms





Bruce IA, Ezgü FS, Kampmann C, Kenis V, Mackenzie W, Stevens B, Walker R, Hendriksz C. Addressing the need for patient-friendly medical communications: adaptation of the 2019 recommendations for the management of MPS VI and MPS IVA. Orphanet J Rare Dis. 2022 Mar 2;17(1):91.

General anesthetics , ENT and respiratory care



Bruce IA, Ezgü FS, Kampmann C, Kenis V, Mackenzie W, Stevens B, Walker R, Hendriksz C. Addressing the need for patient-friendly medical communications: adaptation of the 2019 recommendations for the management of MPS VI and MPS IVA. Orphanet J Rare Dis. 2022 Mar 2;17(1):91.

Summary

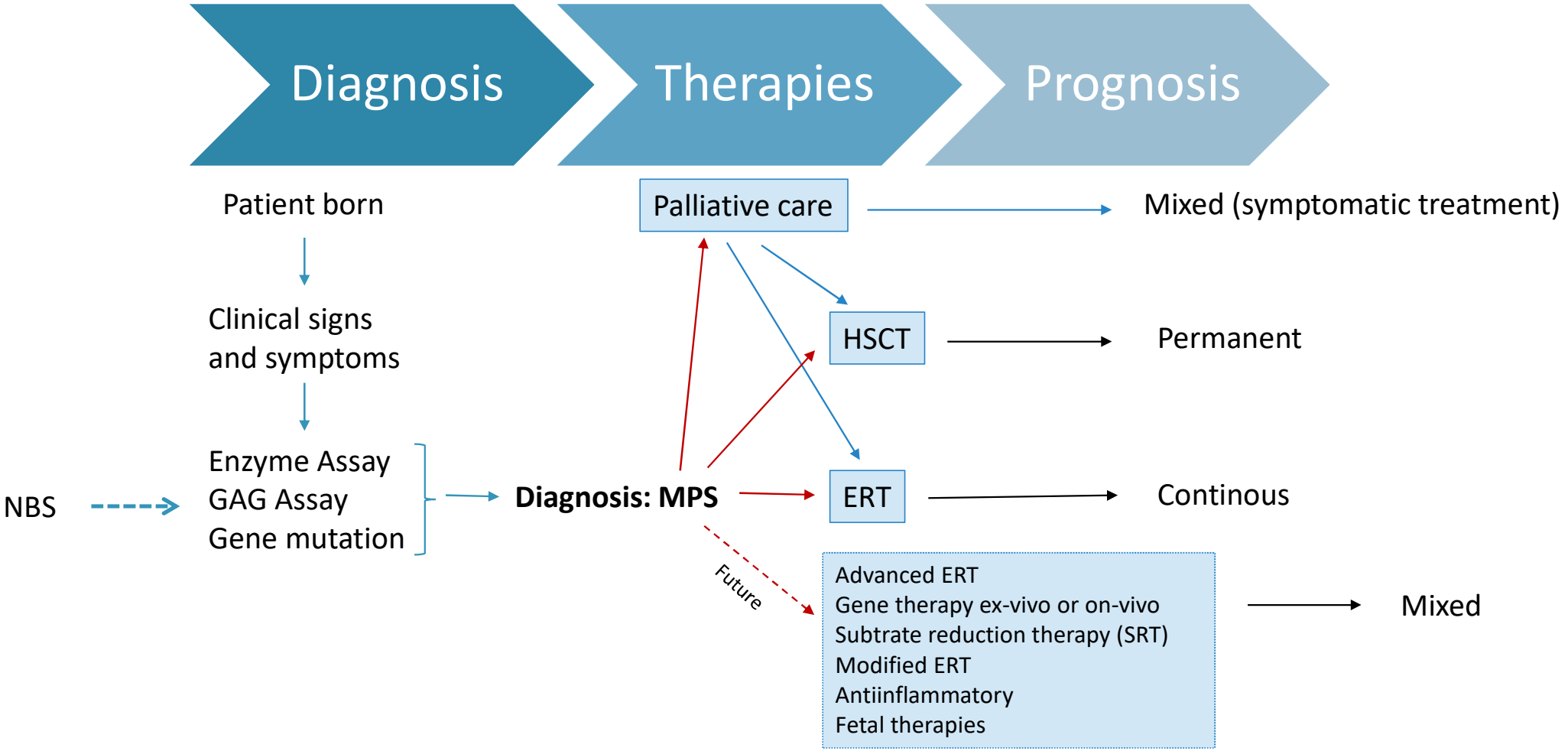
- Optimal treatment starts with early diagnosis
- It is a combination of medical care, psychological, legal, and psychosocial care
- For medical treatment, regular follow up assessemts and symptomatic treatment is essential
  - life threatening disease complications
  - quality of life reducing disease complications

A multidisciplinary team is needed

- Baseline assessments should be performed immediately after diagnosis
- enzyme replacement therapy is available in many countries for all MPSs except MPS III, IVB and IX
- Long term ERT should be started as soon as possible
- HSCT is the standard treatment only in MPS I H < 2.5 years of age
- There is a need of more/new guidelines (covering the different disease severity and age of patients)
- An example for good guidelines are the recommendations for MPS IVA and MPS VI)
- European guidelines for MPS II and international for alpha-mannosidosis are in progress

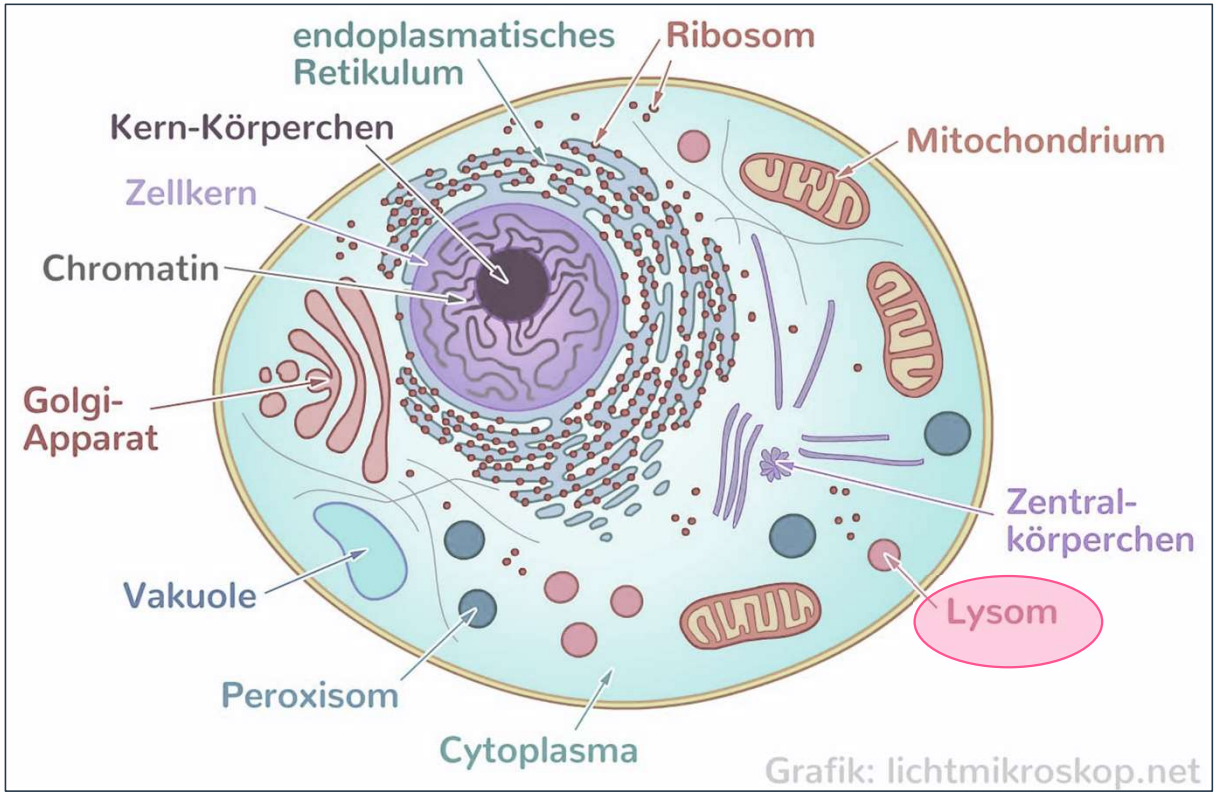
Current and new treatments of MPS patients

Current and future management of MPS disorders



Stapleton M,. Critical review of current MPS guidelines and management. Mol Genet Metab. 2019 Mar;126(3):238-245.

Lysosomes, Recycling stations of the cell



- Lysosomes are cell organelles (spherical vesicles)
- They contain many different digestive enzymes with which they break down foreign substances or endogenous substances
- = Recycling station of the cell
- The enzymes only achieve high activity in an acidic environment
- This ensures that enzymes that enter the cell from damaged lysosomes do not break down important cellular components.

https://www.lichtmikroskop.net/zellen/

MPS Pathophysiology

- **Gene mutation => deficiency of a lysosomal enzyme => storage of glycosaminoglycans in lysosomes.**
- MPS pathophysiology is the result of a complex cascade of secondary events that lead to dysfunction of several cellular processes and pathways:

abnormal composition of membranes

impaired mitochondrial function

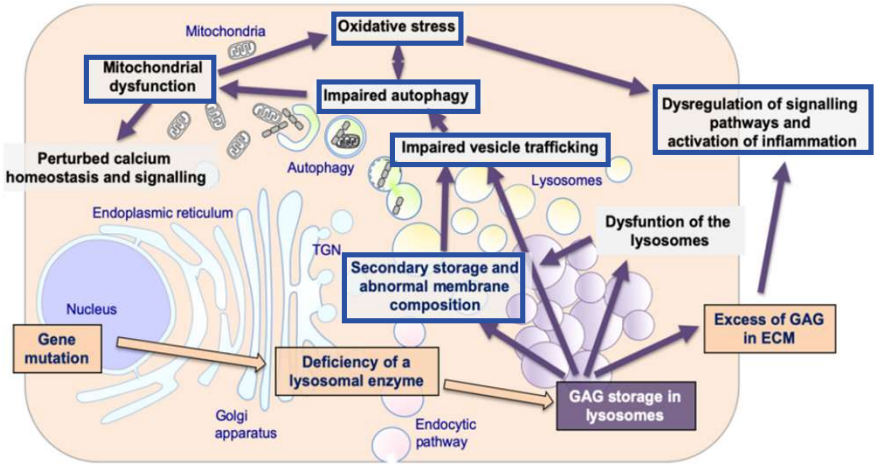
impact on vesicle fusion and trafficking

dysregulation of signaling pathways

impairment of autophagy

oxidative stress

secondary storage of substrates



Adapted from Fecarotta S, Tarallo A, Damiano C, Minopoli N, Parenti G. Pathogenesis of Mucopolysaccharidoses, an Update. Int J Mol Sci. 2020 Apr 4;21(7):2515.

Fecarotta S, Tarallo A, Damiano C, Minopoli N, Parenti G. Pathogenesis of Mucopolysaccharidoses, an Update. Int J Mol Sci. 2020 Apr 4;21(7):2515.

History and treatment in MPS

1881 first described LSD (Tay-Sachs)
1955 Discovery of the lysosome
1963 An enzyme deficiency is described as the cause (alfa-glucosidase in Pompe's disease)
1968 Idea for enzyme replacement therapy (cross correction)

19981 first BMT in MPS I Hurler

1990 first enzyme replacement therapy available (M. Gaucher)

1997 first human ERT trial for MPS began

(10 patients, aged 15-22, were treated with recombinant a-L-iduronidase, and outcomes were measured over one year: significant improvement in peripheral (non-CNS) systemic symptoms: improvements in mobility, increases in linear growth velocity, reductions in liver volume, and reduced urine glycosaminoglycans)

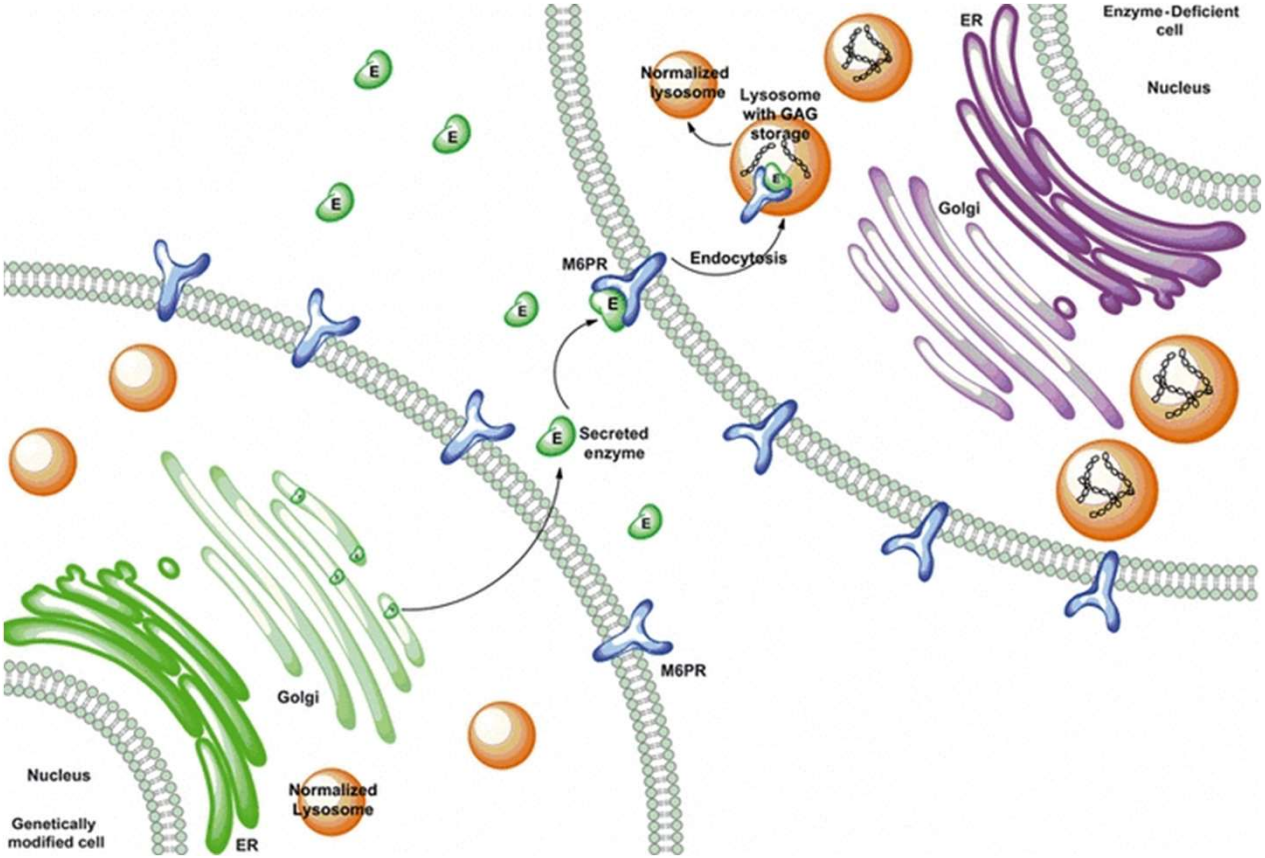
Approvals for enzyme replacement therapies in MPS:
2003 MPS I
2005 MPS VI
2006 MPS II
2014 MPS IV A
2017 MPS VII

By now: no treatment for MPS III (A-D), MPS IVB, and MPS IX available

Penon-Portmann M, Blair DR, Harmatz P. Current and new therapies for mucopolysaccharidoses. Pediatr Neonatol. 2023 Feb;64 Suppl 1:S10-S17.

Enzyme replacement therapy

Principle of ERT: Correction factor



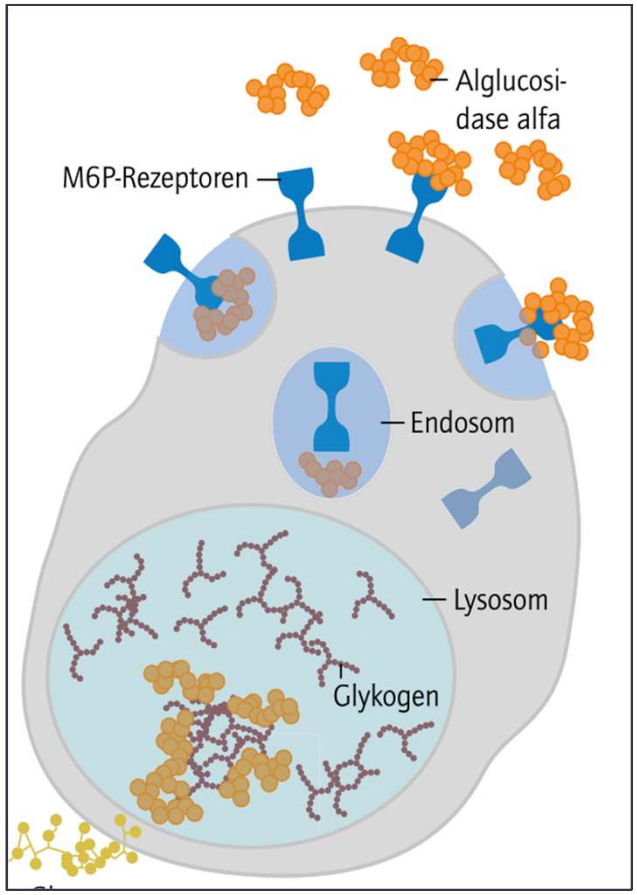
Eine Zelle gibt der anderen ihr funktionierendes Enzym ab und „heilt“ die Zelle

Enzyme replacement therapy using the example of alglucosidase alfa (M. Pompe)

Receptor binding
Enzyme binds to
Mannose-6-phosphate receptor

Endocytosis
Enzyme M6P receptor complex into the cell
Transfer into the lysosomes via endosomes

Substrate cleavage
Degradation of the accumulated substrate by the enzyme
(here glycogen in glucose)



Wenninger S., AMT, 34. Jahrgang Heft 9, Spet 2016

Current treatment options for MPS- enzyme replacement therapy

Table 2 Enzyme replacement therapy summary.

	MPS I	MPS II				MPS IVA	MPS VI	MPS VII
Enzyme deficiency (gene)	Alpha-L-iduronidase (IDUA)	Iduronidate-2-sulfatase (IDS)				N-acetylgalactosamine-6-sulphatase (GALNS)	N-acetylgalactosamine-4-sulphatase (ARSB)	Beta-glucoronidase (GUSB)
Drug	Laronidase	Recombinant idursulphase	Recombinant iduronate-2-sulfatase	Recombinant idursulphase-beta	Recombinant idursulphase-beta	Recombinant elosulphase-alpha	Galsulphase	Vestronidase alfa
	Aldurazyme®, Genzyme.	Elaprase®, Takeda.	IZCARGO®, JCR Pharma	Hunterase® IV, CANbridge	Hunterase® ICV, GC Pharma.	Vimizim®, BioMarin	Naglazyme®, BioMarin	MEPSEVII®, Ultragenyx
	Available since 2003.	Available since 2006.	Available since 2021.	Available since 2012. Approved in Republic of Korea[a]	Available since 2021. Approved in Japan.	Available since 2014.	Available since 2005.	Available since 2017 in the USA.
Dosage	0.58 mg/kg, once a week. Delivered in 3–4 h.	0.5 mg/kg, once a week. Delivered over 3 h, can be shortened to 1 h if no reactions.	2.0 mg/kg/dose, once every 2 weeks.	0.5 mg/kg/dose, once a week	0.5 mg/kg/dose ICV, every 4 weeks	2 mg/kg, once a week. Delivered over 4 h.	1 mg/kg, once a week. Delivered over 4 h.	4 mg/kg, once every 2 weeks. Delivered over 4 h.

ICV = intracerebroventricular injection.

[a] Hunterase IV is also approved in more than 10 countries worldwide.

Penon-Portmann M, Blair DR, Harmatz P. Current and new therapies for mucopolysaccharidoses. Pediatr Neonatol. 2023 Feb;64 Suppl 1:S10-S17. c

Pros and cons of common ERT

pros	cons
Short half life in circulation	Life long therapy
Quick binding to M6P receptors	Weekly or biweekly i.v. infusions 3-5 h
Good penetration of liver, spleen, kidney	Less penetrating bone, cartilage , ocular tissues
-	**Not crossing BBB**
Home treatment possible	Has to be started in hospital setting
Generally well tolerated	Can cause immune reactions

Need of advanced therapies

Outcome ERT: improvements in endurance, pulmonary function, joint mobility

70% of MPS patients have cns involvement

Penon-Portmann M, Blair DR, Harmatz P. Current and new therapies for mucopolysaccharidoses. Pediatr Neonatol. 2023 Feb;64 Suppl 1:S10-S17.

Routes of enzyme replacement administration

Intravenous crossing the bbb

exogenous enzyme is fused to an antibody or peptide that binds to an endothelial receptor, which facilitates its transfer across the bbb

MPS I and II:
Bind the insulin receptor- no efficacy demonstrated

MPSII:
Bind the transferrin receptor
Phase I/II studies underway (2)
Phase II/III study in US and Europe
Approved in Japan

Intrathecal/intracerebroventicular

MPSII:
Intrathecal Idursulfase:
Phase II/III studies– did mot met primary endpoint

Intracerebroventricular Idursulfase beta:
Phase I/II- approval in Japan

MPSIIIA:
Intrathecal rhHNS – did not met the primary endpoint

MPS IIIB:
Intracerebroventricular ERT for MPS IIIB, did not met primary endpoint

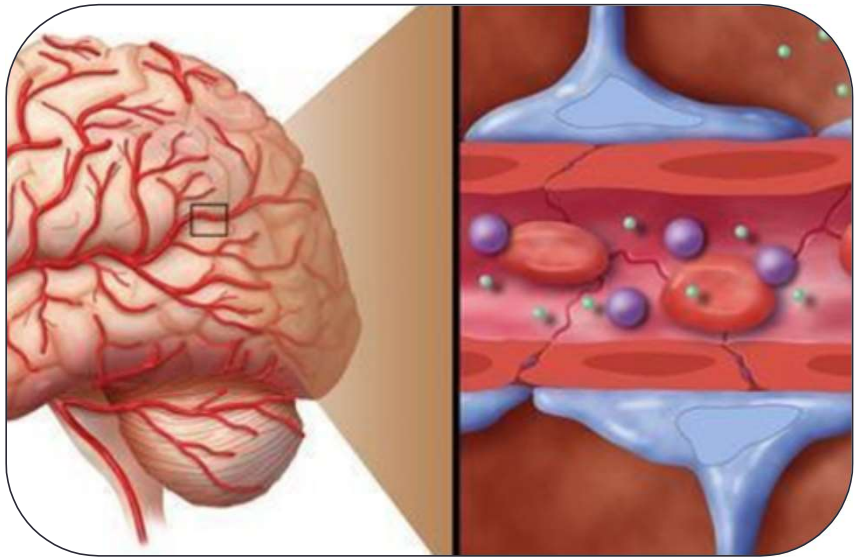
MPSI:
Intrathecal after HSCT- ongoing

Penon-Portmann M, Blair DR, Harmatz P. Current and new therapies for mucopolysaccharidoses. Pediatr Neonatol. 2023 Feb;64 Suppl 1:S10-S17.

Advanced enzyme replacement therapy

The Blood-Brain Barrier

600 km – includes the system of blood vessels that run through the brain



Blood-brain barrier

Blood vessel

Blood-brain barrier

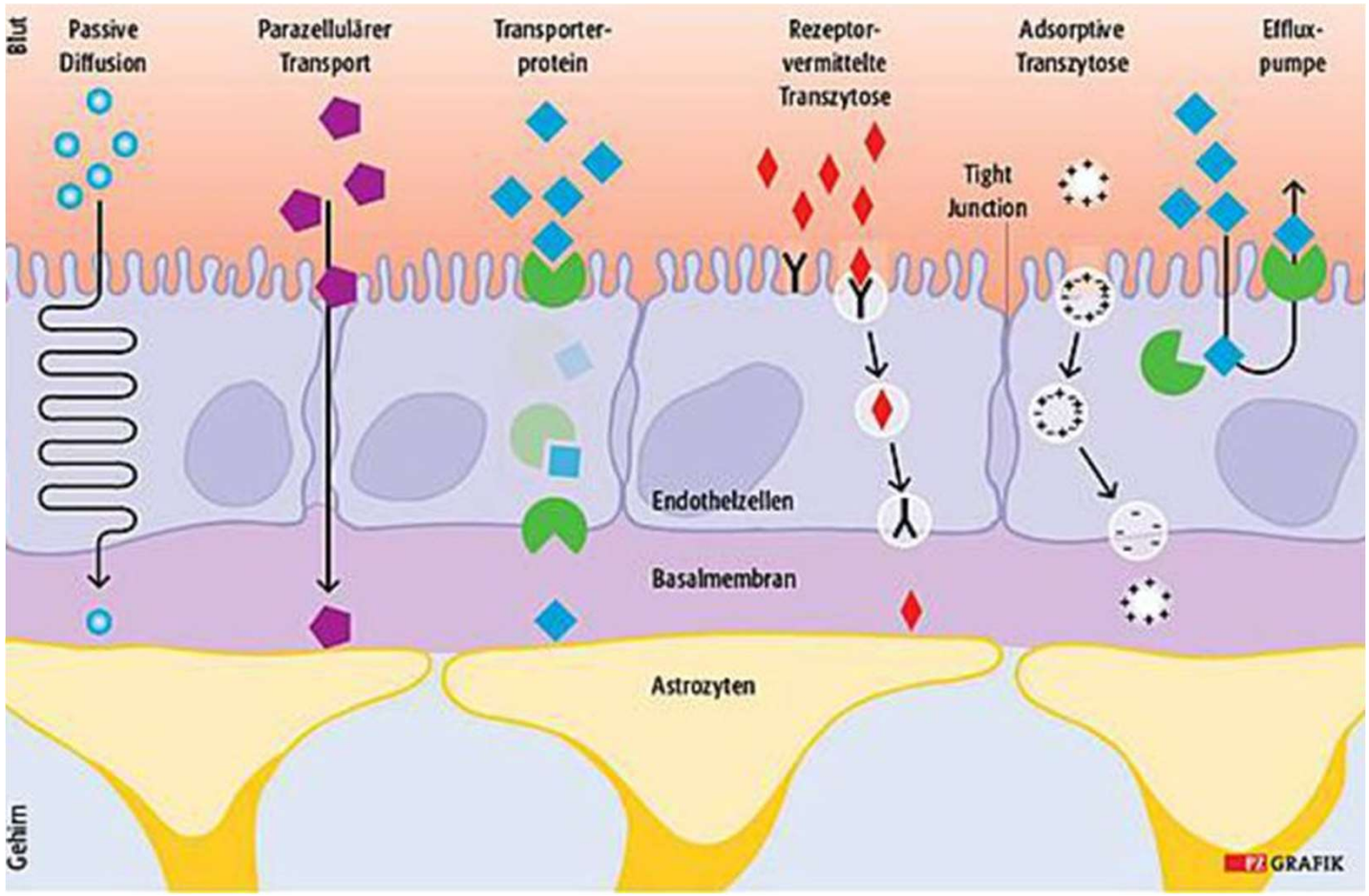
Nerve tissue

Tasks:

- safe functioning of the central nervous system
- Supply of nutrients
- Isolation from foreign substances (including medicines), toxic metabolites and pathogens
- Protection of brain cells from fluctuating concentrations of hormones and messenger substances, changes in the pH of the blood

https://www.stuttgarter-zeitung.de/inhalt.medizin-die-huerde-im-kopf-ueberwinden.c381d023-03f7-4ad9-a6ad-1a05547b9e62.html

Transport routes through the blood-brain barrier



1. passive Diffusion:
Passing through directly

2. Paracellular transport
Transport between the cells

3. Transport proteins
Like a taxi

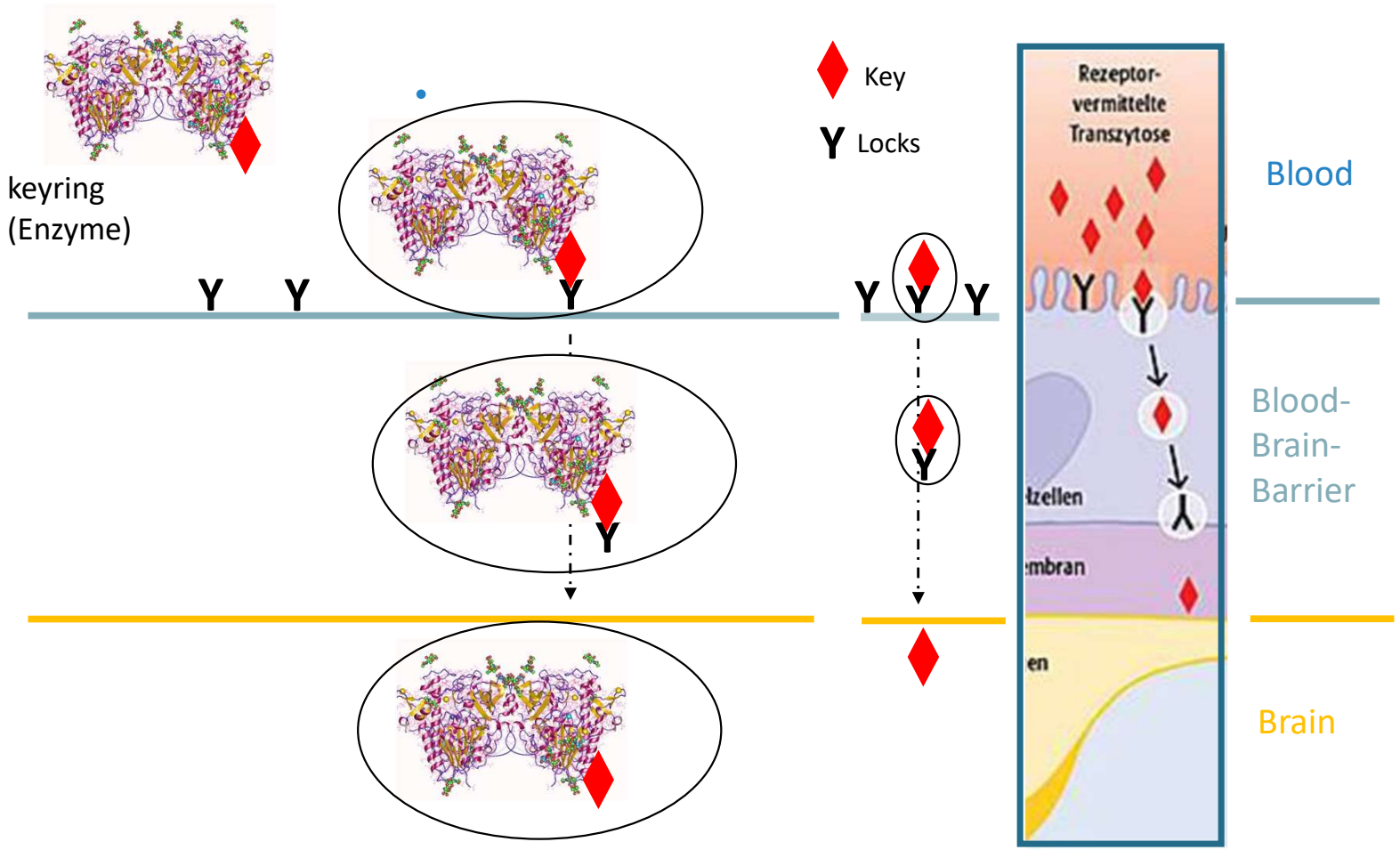
4. Rezeptormediated transcytosis

5. Adsorptive Transcytosis
electrostatic interactions to pass through

6. Effux-Pump
Aktive transport

https://www.pharmazeutische-zeitung.de/ausgabe-282018/wie-arzneistoffe-die-barriere-ueberwinden/

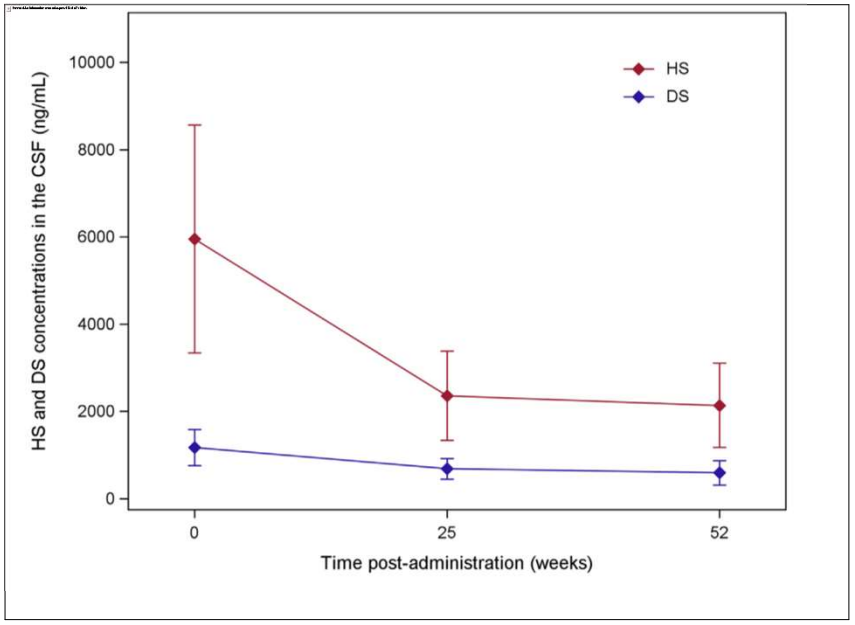
Advanced ERT: Receptor-mediated transport through the blood-brain barrier



https://www.pharmazeutische-zeitung.de/ausgabe-282018/wie-arzneistoffe-die-barriere-ueberwinden/

Exogenous enzyme replacement therapy (JCR) phase II/III in MPS II

- Crossing bbb: transcytosis via transferrin receptors (Trojan horse)
- Multicenter, single arm phase II/III study, n= 28, 2mg/kg pabinafusp over 52 weeks
- Primary endpoint: heparan sulfate in csf
- Secondary endpoints: neurocognitive development, heparan and dermatan in plasma



- 53% adverse events and reactions (mild/moderate)
- Significant decrease in HS
- Positive neurocognitive development in 21/28 patients
- Reduced liver and spleen volume

Ongoing phase III study in US and EU
Ongoing phase I/II study from Denali in US and EU

Okuyama T, Eto Y, Sakai N, Nakamura K, Yamamoto T, Yamaoka M, Ikeda T, So S, Tanizawa K, Sonoda H, Sato Y. A Phase 2/3 Trial of Pabinafusp Alfa, IDS Fused with Anti-Human Transferrin Receptor Antibody, Targeting Neurodegeneration in MPS-II. Mol Ther. 2021 Feb 3;29(2):671-679.

Patients demographics and clinical characteristics

Table 1. Patients' Demographics and Clinical Characteristics

		Prior Enzyme Replacement Therapy with Idursulfase					
		None		Administered		All	
Characteristics		N (%)		N (%)		N (%)	
Number of subjects		3		25		28	
Age (years)	0 to 3 years old	2	(66.7)	3	(12.0)	5	(17.9)
	4 to 7 years old	1	(33.3)	8	(32.0)	9	(32.1)
	8 to 19 years old	0	(0.0)	13	(52.0)	13	(46.4)
	20 years and older	0	(0.0)	1	(4.0)	1	(3.6)
	all	3.0 ± 2.0		9.2 ± 5.5		8.6 ± 5.6	
Weight (kg)		17.33 ± 4.12		32.41 ± 14.51		30.79 ± 14.53	
Ethnicity	Asian	3	(100.0)	25	(100.0)	28	(100.0)
Duration of ERT (days)		–		2,077.2 ± 1,476.1		2,077.2 ± 1,476.1	
Idursulfase-related infusion associated reaction	no	–	(–)	11	(44.0)	11	(44.0)
	yes	–	(–)	14	(56.0)	14	(56.0)
Complications	no	2	(66.7)	9	(36.0)	11	(39.3)
	yes	1	(33.3)	16	(64.0)	17	(60.7)
MPS II-related medical history	no	1	(33.3)	6	(24.0)	7	(25.0)
	yes	2	(66.7)	19	(76.0)	21	(75.0)
MPS II-related neurocognitive impairment	no	0	(0.0)	8	(32.0)	8	(28.6)
	yes	3	(100.0)	17	(68.0)	20	(71.4)
Disease phenotype	severe	3	(100.0)	17	(68.0)	20	(71.4)
	attenuated	0	(0.0)	8	(32.0)	8	(28.6)

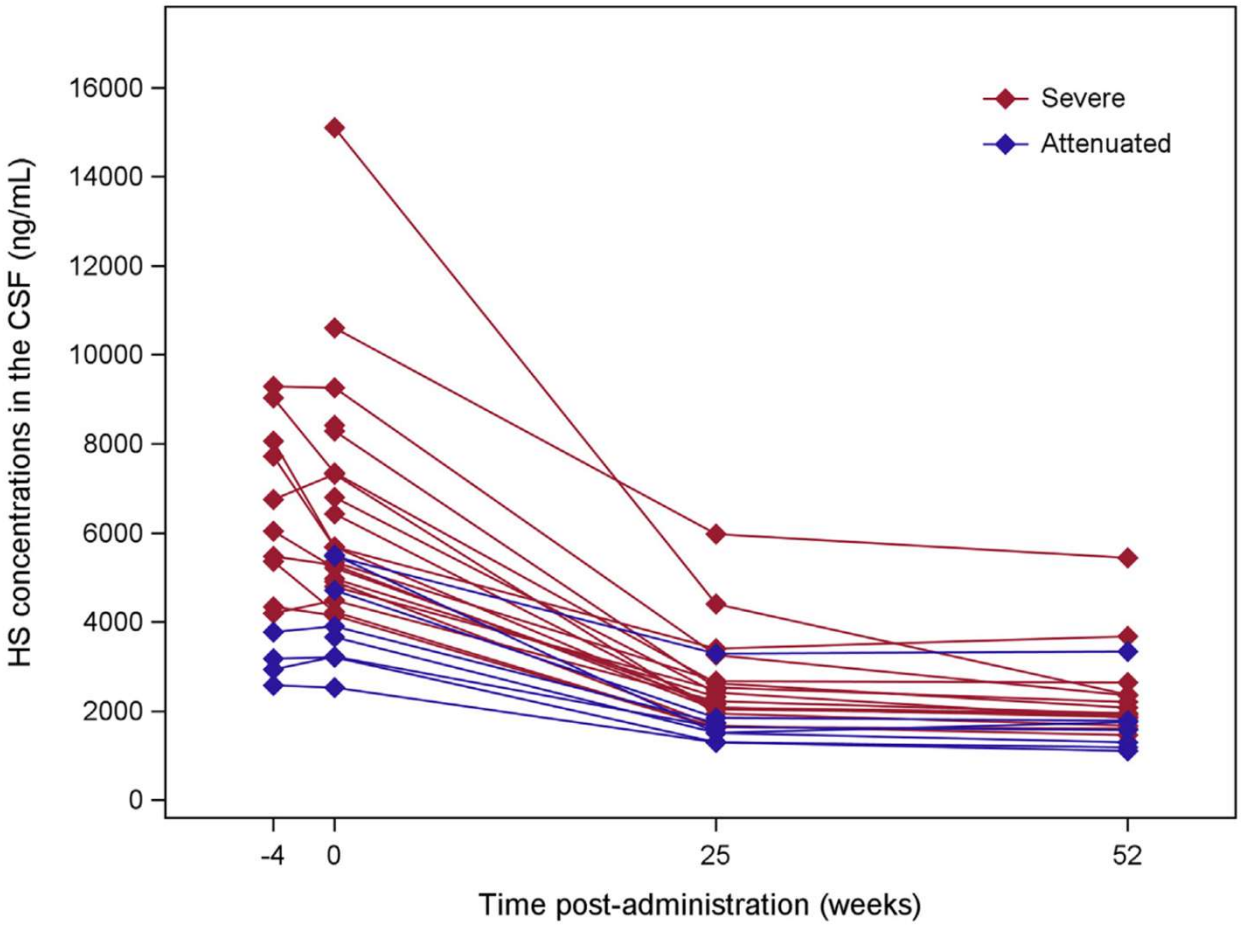
46.4%: 8-19 yrs

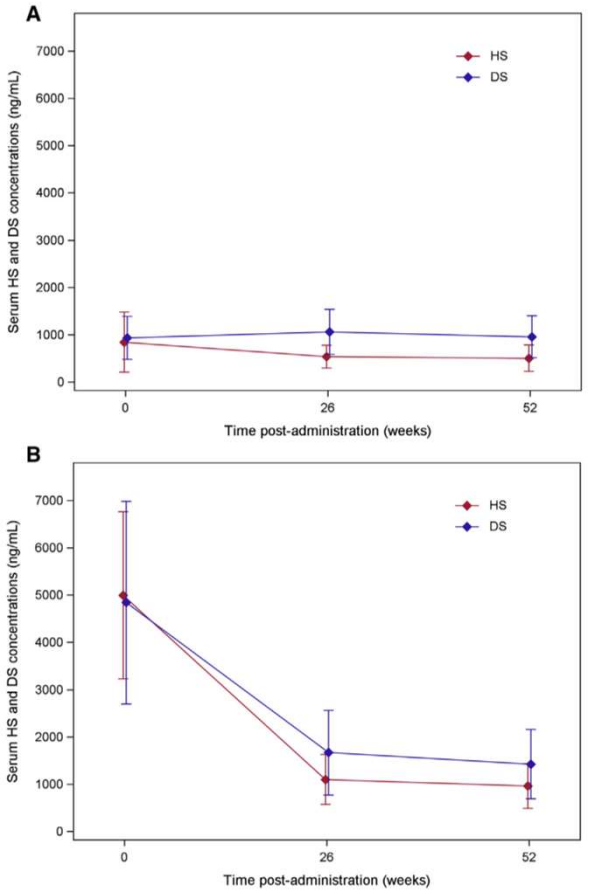
56%: IRR

71.4%: neurocognitive involvement

Okuyama T, Eto Y, Sakai N, Nakamura K, Yamamoto T, Yamaoka M, Ikeda T, So S, Tanizawa K, Sonoda H, Sato Y. A Phase 2/3 Trial of Pabinafusp Alfa, IDS Fused with Anti-Human Transferrin Receptor Antibody, Targeting Neurodegeneration in MPS-II. Mol Ther. 2021 Feb 3;29(2):671-679.

Results: Heparan and dermatan concentrations in csf and serum





Patients prior on ERT

Naiive patients

Okuyama T, Eto Y, Sakai N, Nakamura K, Yamamoto T, Yamaoka M, Ikeda T, So S, Tanizawa K, Sonoda H, Sato Y. A Phase 2/3 Trial of Pabinafusp Alfa, IDS Fused with Anti-Human Transferrin Receptor Antibody, Targeting Neurodegeneration in MPS-II. Mol Ther. 2021 Feb 3;29(2):671-679.

Results neurocognition: change in age aequvalent

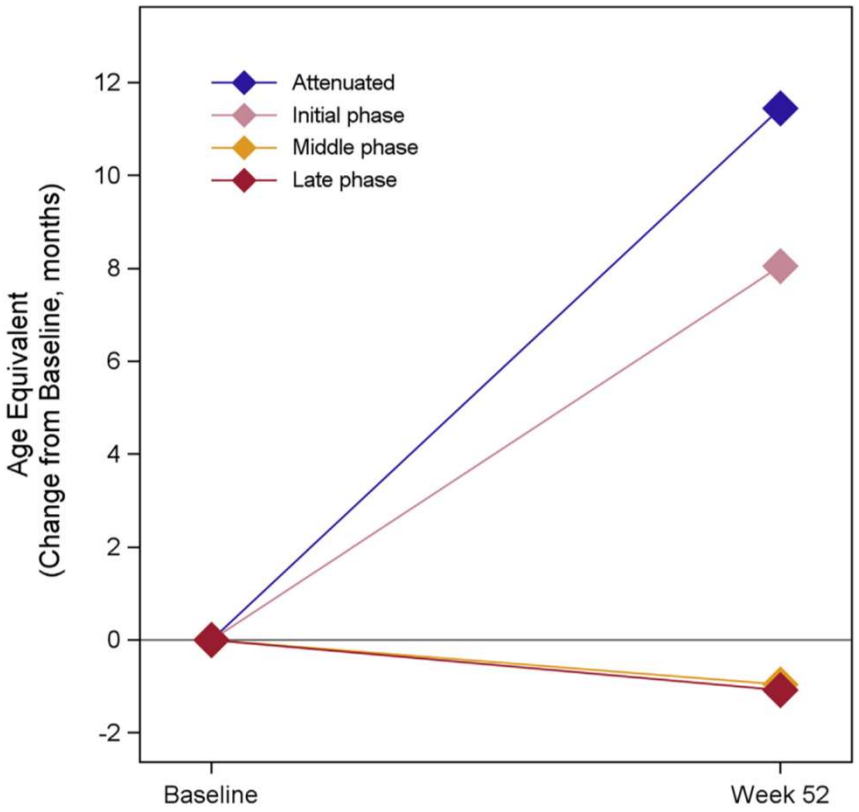
Table 3. The Results of KPSD According to the Four Phenotypes

		Improved		Stabilized		Worsened	
Classification of Disease Phenotype	Total N	Number of Subjects	Proportion (%)	Number of Subjects	Proportion (%)	Number of Subjects	Proportion (%)
Attenuated	8	1	12.5	7	87.5	0	0.0
Severe: initial phase	2	1	50.0	1	50.0	0	0.0
Severe: middle phase	11	1	9.1	7	63.6	3	27.3
Severe: late phase	4	0	0.0	3	75.0	1	25.0

Attenuated: 1/8 improved, 7/8 stabilized
Severe (initial phase): 1/2 improved, 1/2 stabilized
Severe (middle phase): 1/11 improved, 7/11 stabilized, 3/11 worsened
Severe (late phase): 0/4 improved, 3/4 stabilized, 1/4 worsened

Table 2. Criteria for Judgement of Treatment Response at 52 Weeks According to the Kyoto Scale of Psychological Development

Treatment Response/Disease Severity and Clinical Stages	Improvement	Stabilization	Exacerbation
Attenuated	DQ changes > +0.5 SD	DQ changes ± 0.5 SD	DQ changes < −0.5 SD
Severe: initial phase	AE changes > +3 months	AE changes ± 3 months	AE changes < −3 months
Severe: middle phase			
Severe: late phase			



Okuyama T, Eto Y, Sakai N, Nakamura K, Yamamoto T, Yamaoka M, Ikeda T, So S, Tanizawa K, Sonoda H, Sato Y. A Phase 2/3 Trial of Pabinafusp Alfa, IDS Fused with Anti-Human Transferrin Receptor Antibody, Targeting Neurodegeneration in MPS-II. Mol Ther. 2021 Feb 3;29(2):671-679.

Results Pabinafusp alfa: Data from Japan and Brazil

62 patients

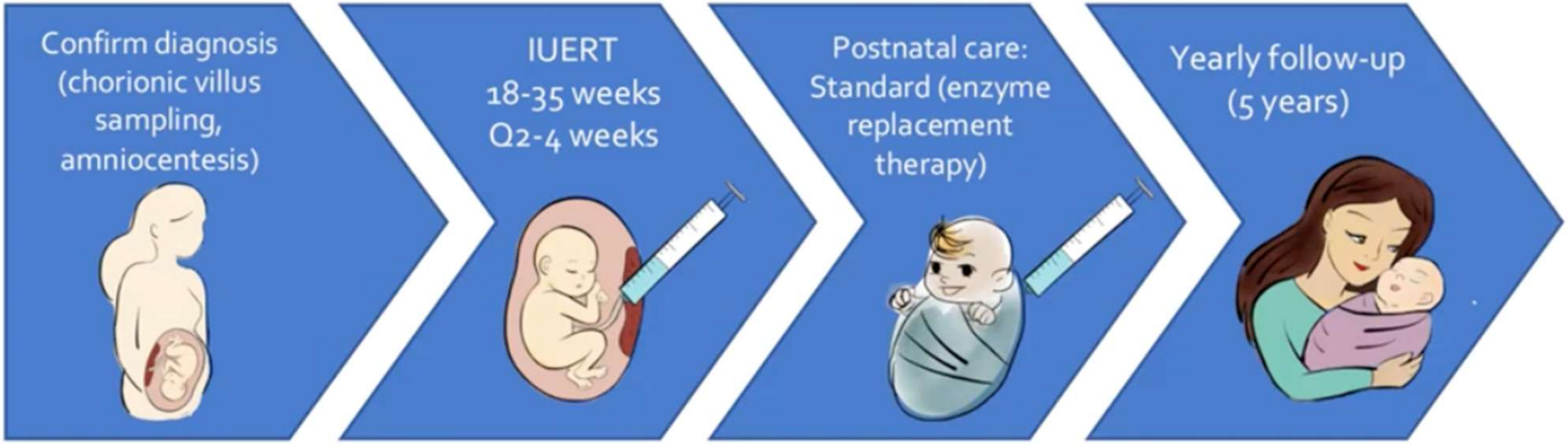
- Japan: 27 patients for 52 weeks and 16 patients for 104 weeks on pabinafusp
- Brazil: 19 patients for 52 weeks and 17 for 104 weeks on pabinafusp

Week	Changes in AE scores	Japan			Brazil			Total
		Severe	Attenuated	Total	Severe	Attenuated	Total	
Week 52	Improvement	2 (11%)	8 (100%)	10 (37%)	8 (57%)	5 (100%)	13 (68%)	23 (50%)
	Stabilization	13 (68%)	0	13 (48%)	5 (36%)	0	5 (26%)	18 (39%)
	Deterioration	4 (22%)	0	4 (15%)	1 (7%)	0	1 (5%)	5 (11%)
Week 104	Improvement	4 (27%)	1 (100%)	5 (31%)	6 (50%)	5 (100%)	11 (65%)	16 (48%)
	Stabilization	5 (33%)	0	5 (31%)	4 (33%)	0	4 (24%)	9 (27%)
	Deterioration	6 (40%)	0	6 (38%)	2 (17%)	0	2 (12%)	8 (24%)

Attenuated patients: Improvement in all patients after 52 and 104 weeks of treatment
Severe patients: stabilization in 39% of patients

Giugliani R, Martins AM, Okuyama T, Eto Y, Sakai N, Nakamura K, Morimoto H, Minami K, Yamamoto T, Yamaoka M, Ikeda T, So S, Tanizawa K, Sonoda H, Schmidt M, Sato Y. Enzyme Replacement Therapy with Pabinafusp Alfa for Neuronopathic Mucopolysaccharidosis II: An Integrated Analysis of Preclinical and Clinical Data. Int J Mol Sci. 2021 Oct 10;22(20):10938.

Intrauterine enzyme replacement therapy (IUERT)



Intrauterine Enzyme replacement therapy (IUERT) phase 1 study

- University of California, San Francisco, USA
- Enzyme administration into the umbilical vein every 2-4 weeks (10 women 18-50 years)
- Diseases: **MPS I, II, IVA, VI, VII,** M. Pompe (IOPD), M. Gaucher (type II and III), LALD (M. Wolman)
- Dose of ERT weight-adjusted to fetal weight => dosage corresponds to recommended weight-based postnatal dosing
- Start: July 21, End: 2031
- Primary endpoint: Safety
- Secondary endpoints: antibody formation against the enzyme, echocardiography, skeletal examination, growth, mobility and neurocognitive functions
- **Rationale:**
- high postnatal morbidity and fetal mortality, especially in the context of NIHF (perinatal mortality rate 30-75%)
- In utero-period: period of relative fetal tolerance to immune stimuli

  => improved response to ERT without development of AK
- Likelihood that IUERT will lead to an improvement in neurological development

Cohen JL, Chakraborty P, Fung-Kee-Fung K, Schwab ME, Bali D, Young SP, Gelb MH, Khaledi H, DiBattista A, Smallshaw S, Moretti F, Wong D, Lacroix C, El Demellawy D, Strickland KC, Lougheed J, Moon-Grady A, Lianoglou BR, Harmatz P, Kishnani PS, MacKenzie TC. In Utero Enzyme-Replacement Therapy for Infantile-Onset Pompe's Disease. N Engl J Med. 2022 Dec 8;387(23):2150-2158.

Intrauterine enzyme replacement therapy: first in Pompe disease

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

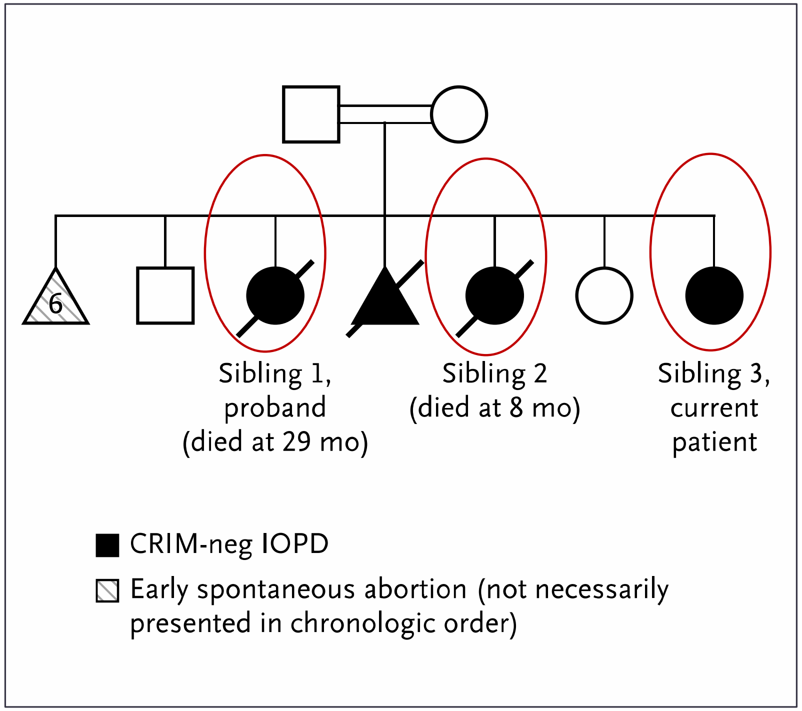
In Utero Enzyme-Replacement Therapy for Infantile-Onset Pompe's Disease

Jennifer L. Cohen, M.D., Pranesh Chakraborty, M.D., Karen Fung-Kee-Fung, M.D., Marisa E. Schwab, M.D., Deeksha Bali, Ph.D., Sarah P. Young, Ph.D., Michael H. Gelb, Ph.D., Hamid Khaledi, Ph.D., Alicia DiBattista, Ph.D., Stacey Smallshaw, R.N., Felipe Moretti, M.D., Derek Wong, M.D., Catherine Lacroix, P.T., Dina El Demellawy, M.D., Ph.D., Kyle C. Strickland, M.D., Ph.D., Jane Lougheed, M.D., Anita Moon-Grady, M.D., Billie R. Lianoglou, M.S., Paul Harmatz, M.D., Priya S. Kishnani, M.D., and Tippi C. MacKenzie, M.D.

Cohen JL, Chakraborty P, Fung-Kee-Fung K, Schwab ME, Bali D, Young SP, Gelb MH, Khaledi H, DiBattista A, Smallshaw S, Moretti F, Wong D, Lacroix C, El Demellawy D, Strickland KC, Lougheed J, Moon-Grady A, Lianoglou BR, Harmatz P, Kishnani PS, MacKenzie TC. In Utero Enzyme-Replacement Therapy for Infantile-Onset Pompe's Disease. N Engl J Med. 2022 Dec 8;387(23):2150-2158.

Pedigree of the family

37-year-old 12 gravida 4 para, 2 healthy children, 6 early abortions (3 with IOPD)



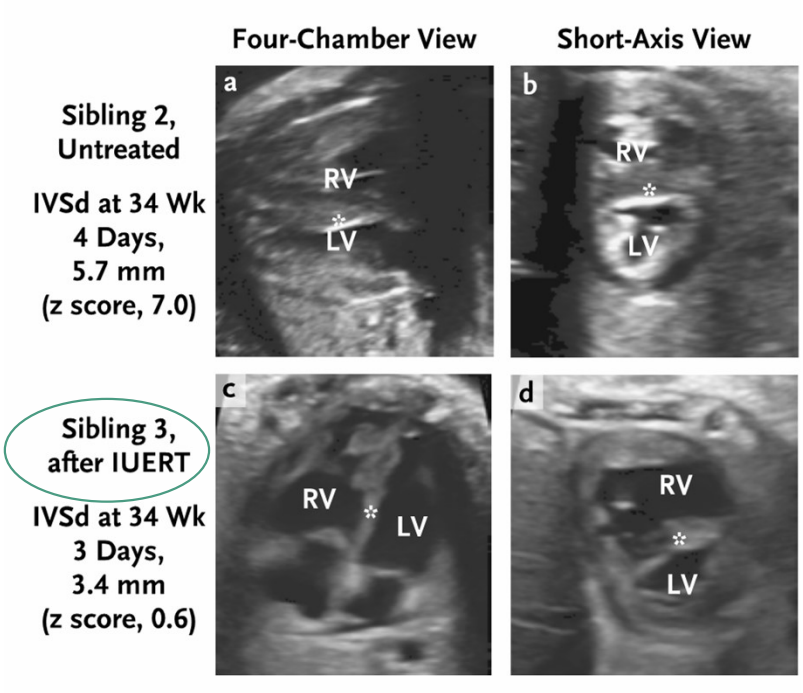
Sib 1:
Diagnosis at 3.9 months
CRIM neg: => immunomodulation
Start ERT (GAA) with 6.0 months standard dose
Stop ERT at 24 months
Death at 29 months

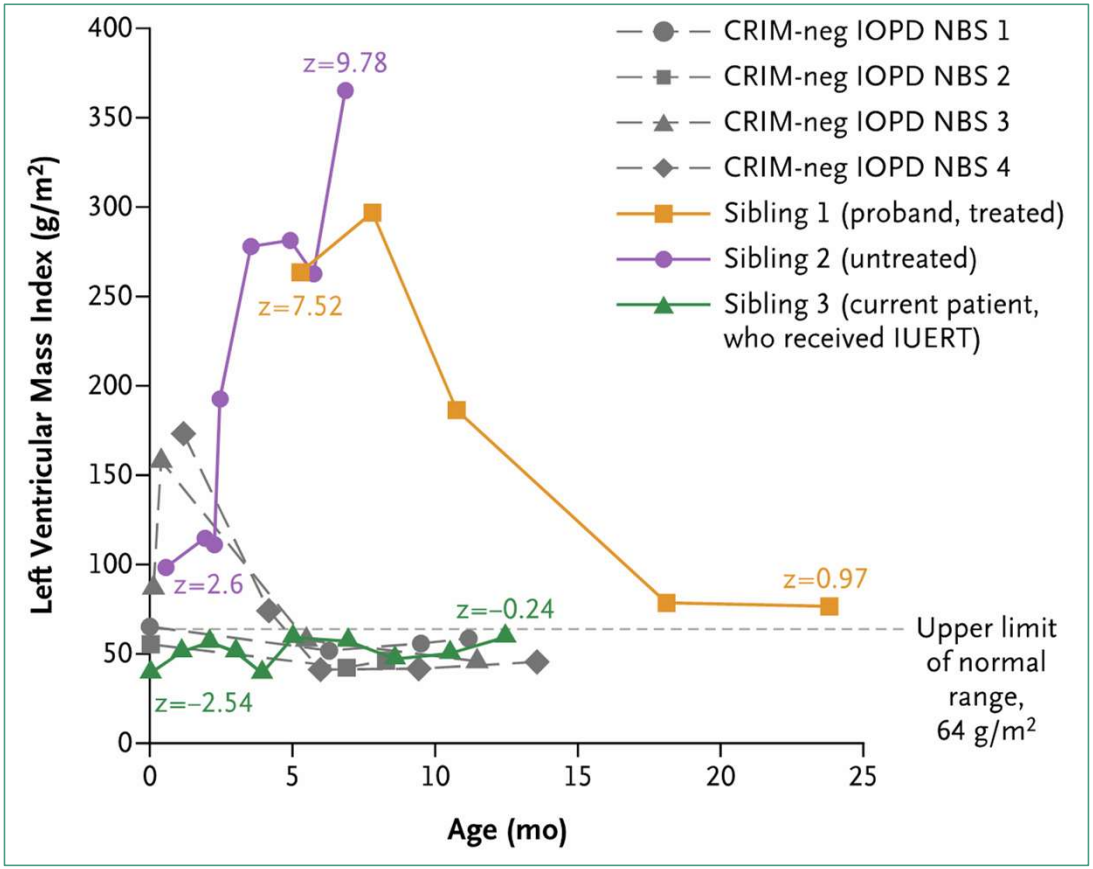
Sib 2:
Prenatal diagnosis
With already hypertrophic cardiomyopathy
Postnatal (no bed) control
CRIM neg: Immunomodulation
Muscular hypotonia
Difficulty breathing at 2 months
Palliative care
Death at 8 months

Sib 3:
Prenatal diagnosis
Start IUERT week 24+5 to 34+5 (6 infusions)
Standard dosage Alglucosidase alpha every 2 weeks
Vaginal birth 37+4
Postnatal:
Day 1 Immunomodulation
From day 4 every 2 weeks ERT with alglucosidase alpha
From 9.6 months, double dose ERT every 2 weeks
From 11.3 months, double dose weekly

Cohen JL, Chakraborty P, Fung-Kee-Fung K, Schwab ME, Bali D, Young SP, Gelb MH, Khaledi H, DiBattista A, Smallshaw S, Moretti F, Wong D, Lacroix C, El Demellawy D, Strickland KC, Lougheed J, Moon-Grady A, Lianoglou BR, Harmatz P, Kishnani PS, MacKenzie TC. In Utero Enzyme-Replacement Therapy for Infantile-Onset Pompe's Disease. N Engl J Med. 2022 Dec 8;387(23):2150-2158.

Echocardiography findings





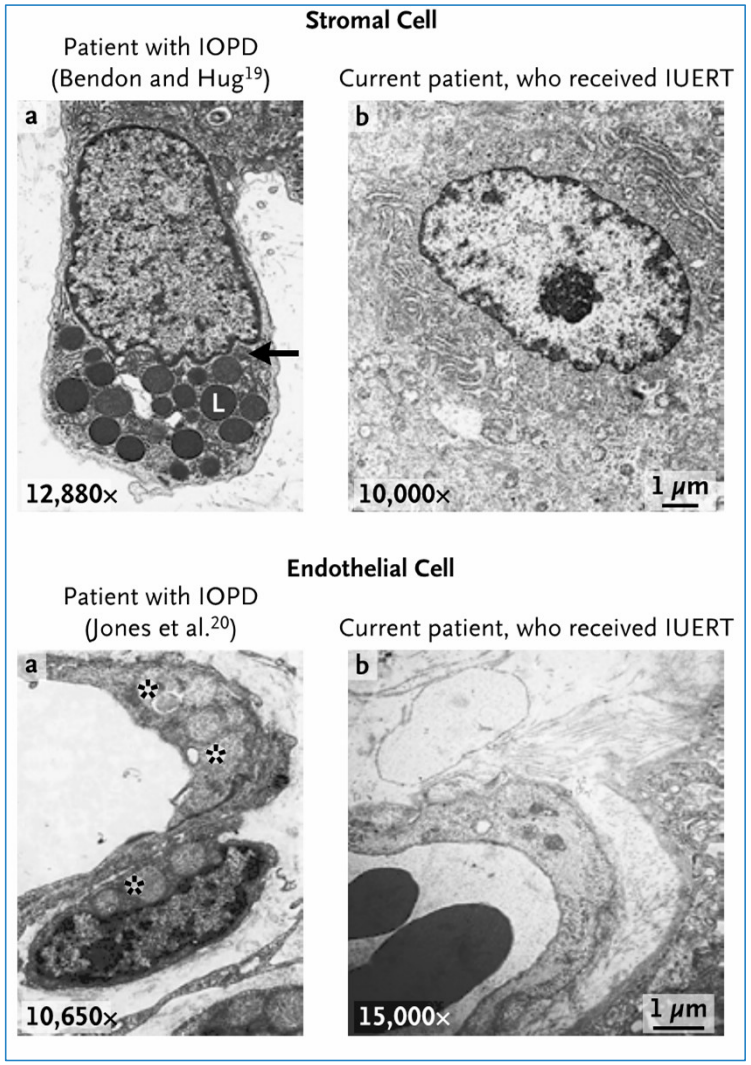
- Decrease in ventricular wall thickness in IUERT-treated Sib3 as opposed to untreated Sib2
- LVMI at Sib 3 in the normal range

Cohen JL, Chakraborty P, Fung-Kee-Fung K, Schwab ME, Bali D, Young SP, Gelb MH, Khaledi H, DiBattista A, Smallshaw S, Moretti F, Wong D, Lacroix C, El Demellawy D, Strickland KC, Lougheed J, Moon-Grady A, Lianoglou BR, Harmatz P, Kishnani PS, MacKenzie TC. In Utero Enzyme-Replacement Therapy for Infantile-Onset Pompe's Disease. N Engl J Med. 2022 Dec 8;387(23):2150-2158.

Electron microscopic examination of the placenta

Arrow:
membrane-bound glycogen lobules
Unbound cytoplasmic glycogen rosetts

IOPD Patients

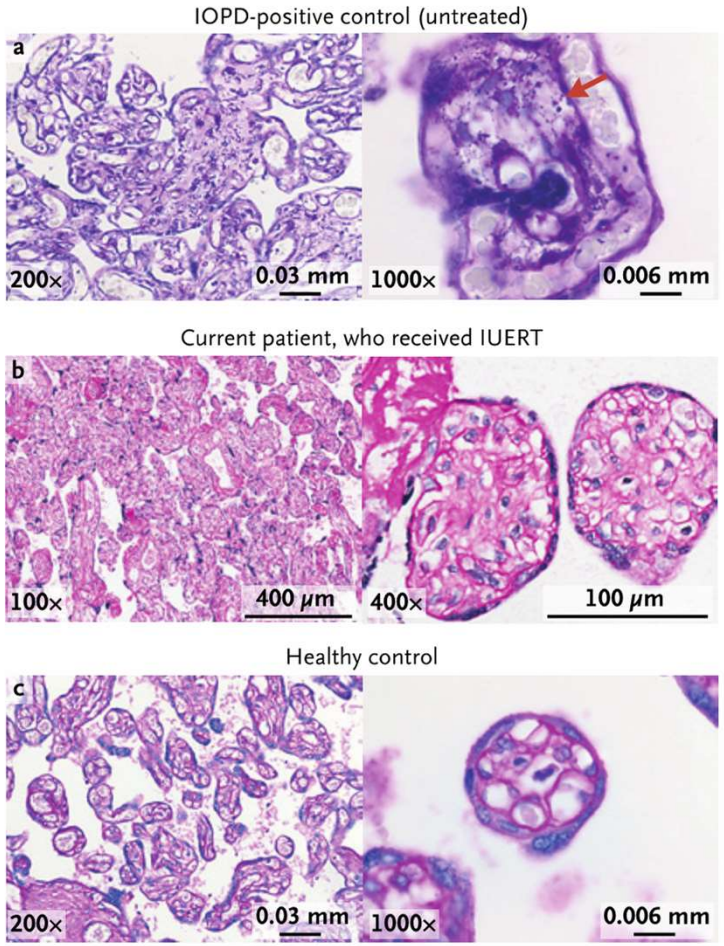


Sib 3
No glycogen storage

Asterisk:
glycogen-filled lysosomes

Cohen JL, Chakraborty P, Fung-Kee-Fung K, Schwab ME, Bali D, Young SP, Gelb MH, Khaledi H, DiBattista A, Smallshaw S, Moretti F, Wong D, Lacroix C, El Demellawy D, Strickland KC, Lougheed J, Moon-Grady A, Lianoglou BR, Harmatz P, Kishnani PS, MacKenzie TC. In Utero Enzyme-Replacement Therapy for Infantile-Onset Pompe's Disease. N Engl J Med. 2022 Dec 8;387(23):2150-2158.

Light microscopic examination of the placenta (PAS staining)



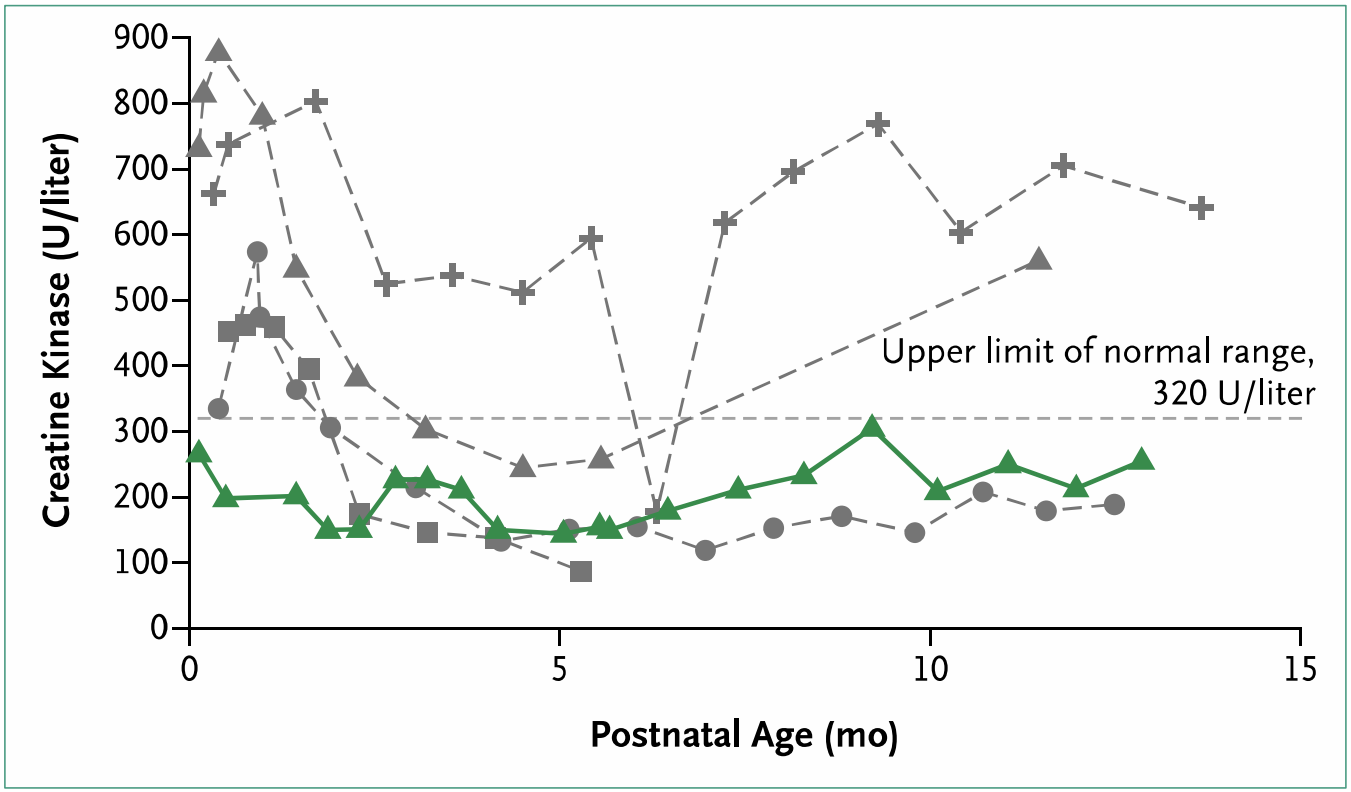
Untreated IOPD patient
PAS positive granules

Current Patient (IUERT) Sib3
No Ganula

Healthy control

Cohen JL, Chakraborty P, Fung-Kee-Fung K, Schwab ME, Bali D, Young SP, Gelb MH, Khaledi H, DiBattista A, Smallshaw S, Moretti F, Wong D, Lacroix C, El Demellawy D, Strickland KC, Lougheed J, Moon-Grady A, Lianoglou BR, Harmatz P, Kishnani PS, MacKenzie TC. In Utero Enzyme-Replacement Therapy for Infantile-Onset Pompe's Disease. N Engl J Med. 2022 Dec 8;387(23):2150-2158.

CK range at CRIM neg. IOPD patients (treated from 4th day of life ERT) compared to IUERT patient Sib 3

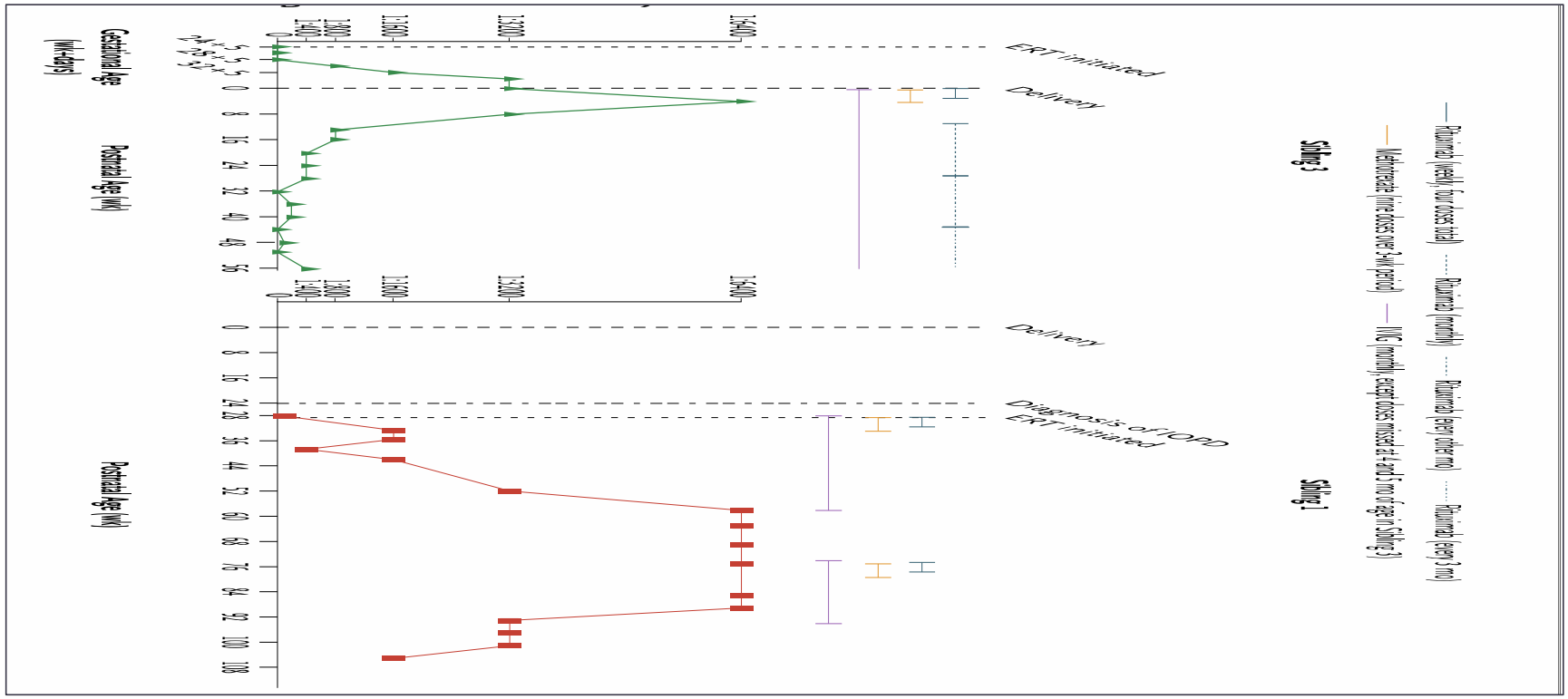


IUERT Sib 3

CRIM-neg IOPD NBS 1
CRIM-neg IOPD NBS 2
CRIM-neg IOPD NBS 3
CRIM-neg IOPD NBS 5
Sibling 3 (current patient, who received IUERT)

Cohen JL, Chakraborty P, Fung-Kee-Fung K, Schwab ME, Bali D, Young SP, Gelb MH, Khaledi H, DiBattista A, Smallshaw S, Moretti F, Wong D, Lacroix C, El Demellawy D, Strickland KC, Lougheed J, Moon-Grady A, Lianoglou BR, Harmatz P, Kishnani PS, MacKenzie TC. In Utero Enzyme-Replacement Therapy for Infantile-Onset Pompe's Disease. N Engl J Med. 2022 Dec 8;387(23):2150-2158.

Antibodies



Sib 3: Peak at week 4 postpartum, then drop at week 14

Sib 1: sustained titer at 1:6400 (pharmacokinetic and clinical concerns are present when titers reach a level of > 1:12,800)

Cohen JL, Chakraborty P, Fung-Kee-Fung K, Schwab ME, Bali D, Young SP, Gelb MH, Khaledi H, DiBattista A, Smallshaw S, Moretti F, Wong D, Lacroix C, El Demellawy D, Strickland KC, Lougheed J, Moon-Grady A, Lianoglou BR, Harmatz P, Kishnani PS, MacKenzie TC. In Utero Enzyme-Replacement Therapy for Infantile-Onset Pompe's Disease. N Engl J Med. 2022 Dec 8;387(23):2150-2158.

Summary of IUERT results

6 IUERT Infusionen:

Postnatal observation period up to 13 months:

No AEs

Laboratory:

Normal CK values at birth until the end of the observation period (13 months)

Development:

Normal fine and gross motor development, running at 11.5 months

Heart:

Echocardiography: no LVH, normal LVMI

ECG: normal

Placenta:

Light and electron microscopy: No granules, no glycogen rosettes

Ab development:

from the 3rd IUERT, peak at week 34+5, drop postnatally 8th week (in the clinically non-significant range)

GAA and GLC4

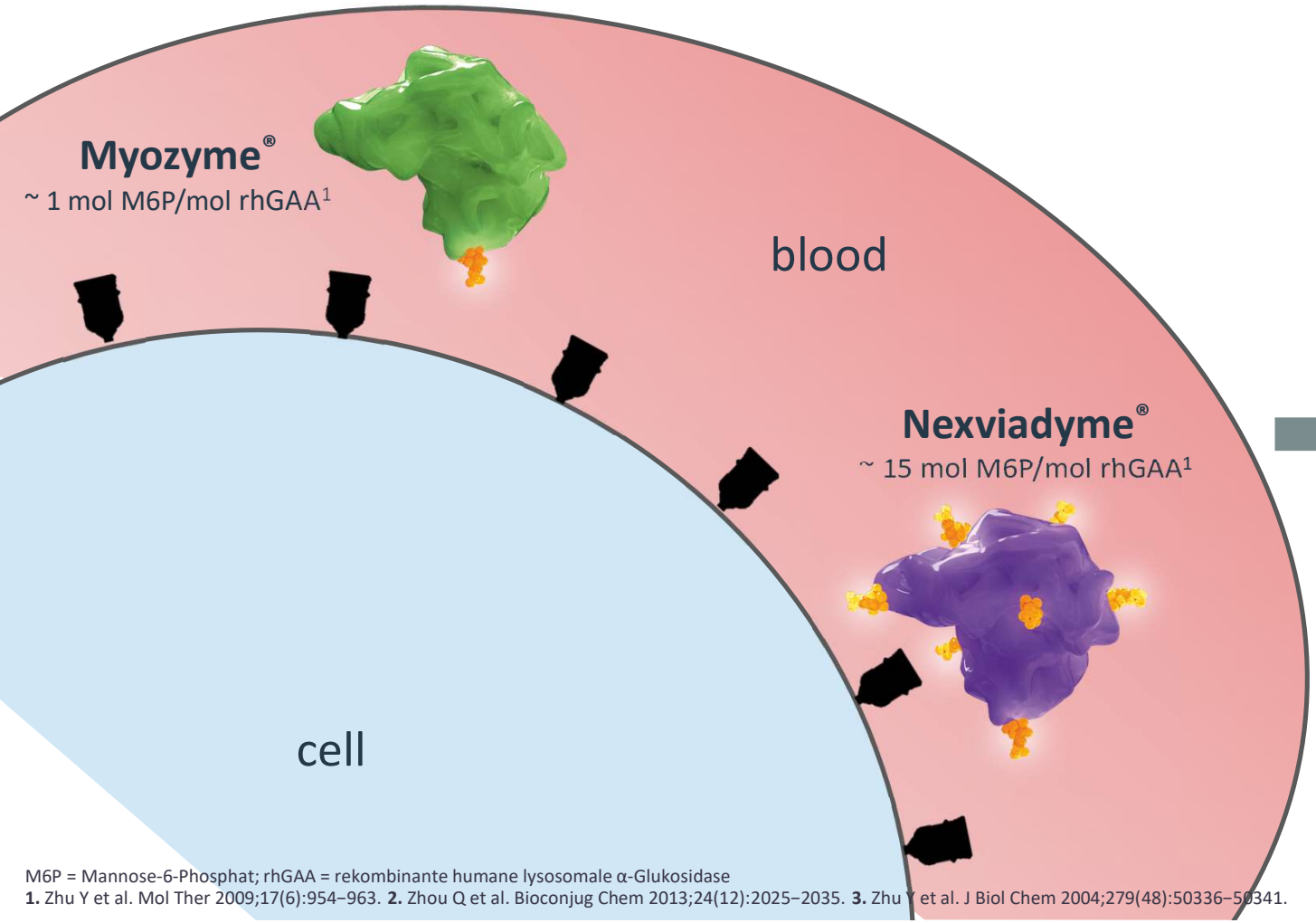
Normalization

IUERT appears to be safe, there is a significant normalization of the examined parameters up to 13 months of age

Cohen JL, Chakraborty P, Fung-Kee-Fung K, Schwab ME, Bali D, Young SP, Gelb MH, Khaledi H, DiBattista A, Smallshaw S, Moretti F, Wong D, Lacroix C, El Demellawy D, Strickland KC, Lougheed J, Moon-Grady A, Lianoglou BR, Harmatz P, Kishnani PS, MacKenzie TC. In Utero Enzyme-Replacement Therapy for Infantile-Onset Pompe's Disease. N Engl J Med. 2022 Dec 8;387(23):2150-2158.

Further ideas to improve ERT

Advanced ERT: increasing M6P receptors (in Pompe disease)

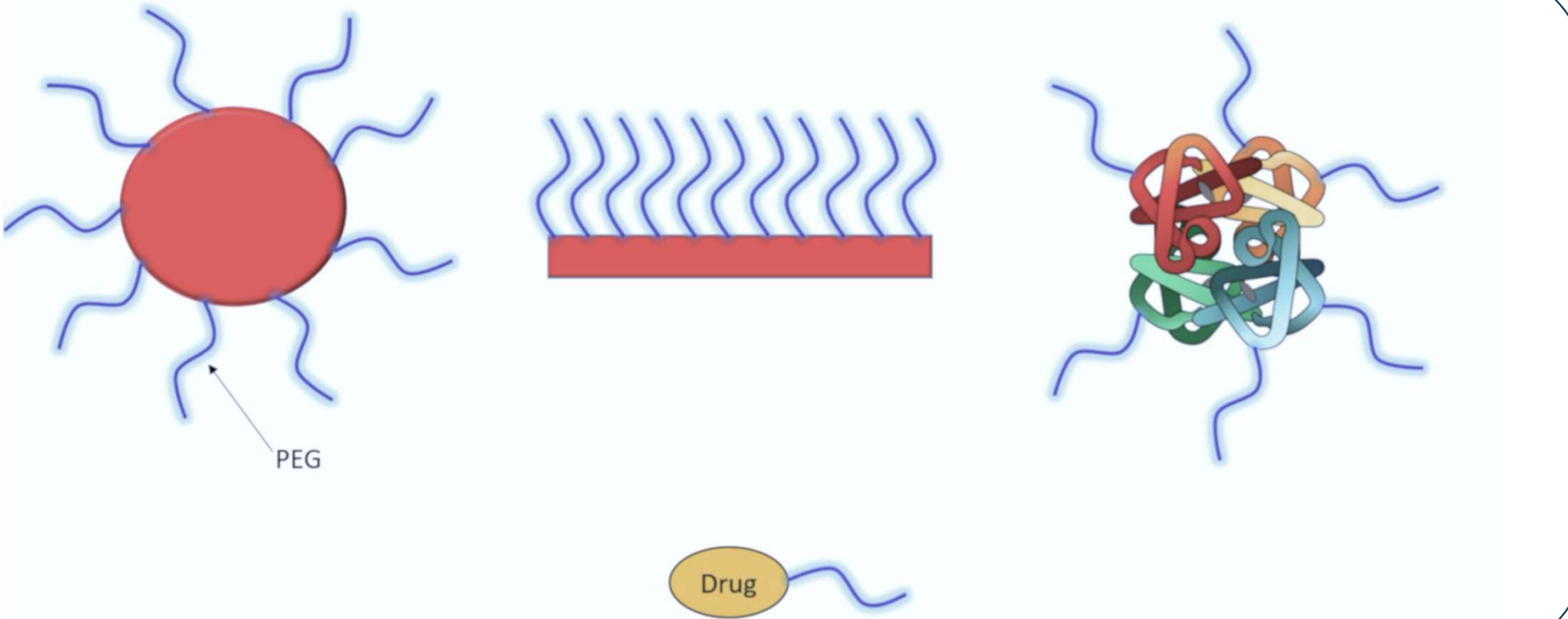


- **~ 1,000x** higher binding affinity to the M6P receptor
- **~ 15x** higher uptake into the myoblasts
- **~ 5x** improved glycogen breakdown

M6P = Mannose-6-Phosphat; rhGAA = rekombinante humane lysosomale α-Glukosidase

1. Zhu Y et al. Mol Ther 2009;17(6):954–963. **2.** Zhou Q et al. Bioconjug Chem 2013;24(12):2025–2035. **3.** Zhu Y et al. J Biol Chem 2004;279(48):50336–50341.

Advanced ERT: PEGylated enzyme leads to longer half-life (longer circulation in blood)



https://www.youtube.com/watch?app=desktop&v=72jz-q6jP54

Hematopoetic stem cell transplantation

Hematopoetic stem cell transplantation (HSCT)

MPS I:

First BMT in an 1 year old Hurler patient 1981 with skeletal abnormalities, coarse face, corneal clouding, hepatosplenomegaly

- Nearly normal Iduronidase activity
- Dropping down of GAG excertion in urine
- Hepatosplenomegaly and occular findings resolved
- arrest of other disease findings
- by now, > 200 MPS I H patients were transplanted
- Survival into andulthood after HSCT (> 50% of patients were alive 10 years after transplantation)
- Stem cells are crossing the BBB: improvement of neurocognition
- Improvemet of musculoskeletal, ocular, cardiac and pulmonary involvement

In MPS I Hurler patients, HSCT is the standard of care when performed > 2.5 yeras of age
Mortality 5-10%

Penon-Portmann M, Blair DR, Harmatz P. Current and new therapies for mucopolysaccharidoses. Pediatr Neonatol. 2023 Feb;64 Suppl 1:S10-S17.

Hematopoetic stem cell transplantation (HSCT)

MPSII:

First BMT in MPS II in 1986

⇒ By now, > 100 MPS II patients were transplanted

⇒ improvement of somatic signs but unclear efficacy of neurocognition

MPS III:

Unclear efficacy on neurodegeneration (too late transplantation?)

Other MPSs:

=> Lack of data, may improve somatic signs

HSCT can induce tolerance (in case of immune intolerance against ERT or gene therapy)
Autologous HSCT can serve as the mechanism of delivery of gene therapy

Penon-Portmann M, Blair DR, Harmatz P. Current and new therapies for mucopolysaccharidoses. Pediatr Neonatol. 2023 Feb;64 Suppl 1:S10-S17.

Gene therapy

History of gene therapy

1953 Discovery of the DNA structure

1961-1966 Discovery of the genetic code

1973 Development of a technique to transer gene material

1980 First gene therapy was tested without permission (did not work)

1990 First gene therapy trial using new viral vector technology

- 2 patients with severe combined immunodeficiency (SCID) received treatment using novel gamma **retrovirus** vector technology. The results were mixed, with 1 modest response and 1 limited response

1999 Gene Therapy Clinical Trial Monitoring Plan and Gene Transfer Safety Symposia

- Jesse Gelsinger, an 18-year-old boy with a relatively mild form of ornithine transcarbamylase (OTC) deficiency, died while participating in an adenoviral gene therapy trial due to a severe immune reaction to the vector. Investigators later found that several other patients had experienced serious side effects after being injected, but Jesse was never informed of them. This caused the FDA and NIH to enhance patient protection through 2 new programs, the Gene Therapy Clinical Trial Monitoring Plan and the Gene Transfer Safety Symposia.

2003 First gene therapy appoved in China (skin cancer)

2012 EMA approved frist AAV based gene therapy for LPLD removed from the market 2017 due to limited use

2017 First gene therapy appoved in USA (ALL)

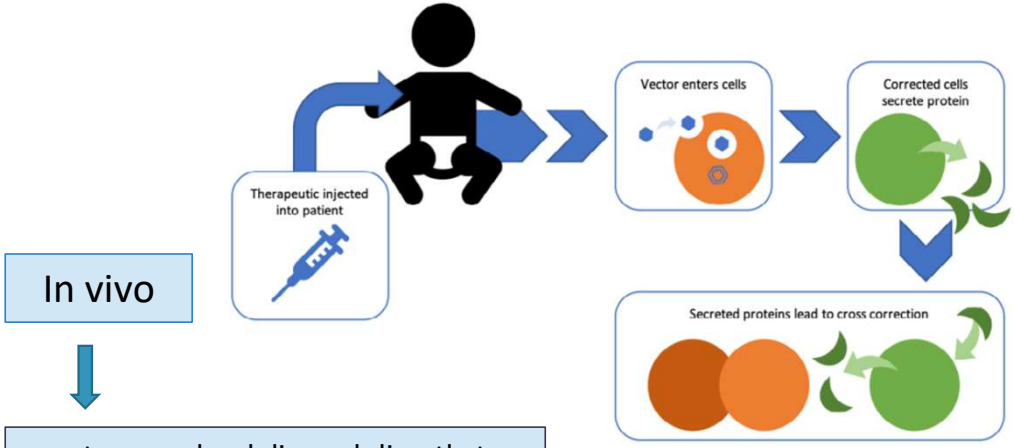
2019 FDA Approval AAV based in vivo gene therapy for SMA (EMA 2020)

2021 Youngest patient (4 day-old-boy) received gene therapy for SMA

24 gene therapies are approved
18 studies in lysosomal diseases

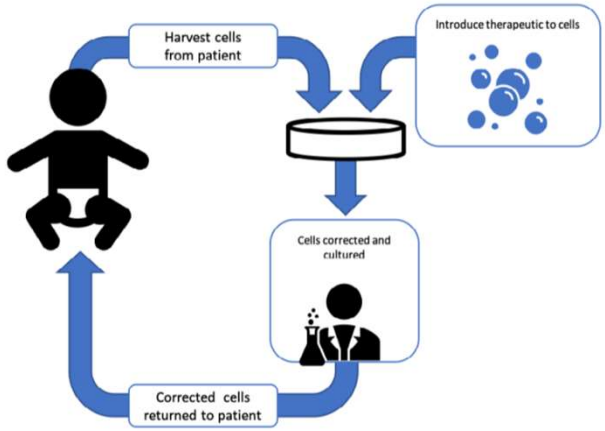
Procedure of gene therapy

- genetic material (genomic DNA, coding DNA or RNA) is inserted into human cells to:
  - 1) correct the underlying molecular error
  - 2) exogenously express the deficient enzyme
- patient's own cells begin producing the desired enzyme, bypassing their underlying metabolic defect
- critical hurdle: delivery
- Typically, done with therapeutically engineered viruses (e.g. modified adeno-associated virus (AAV))



In vivo

vectors can be delivered directly to:
- the CNS (brain or spinal cord)
- bloodstream

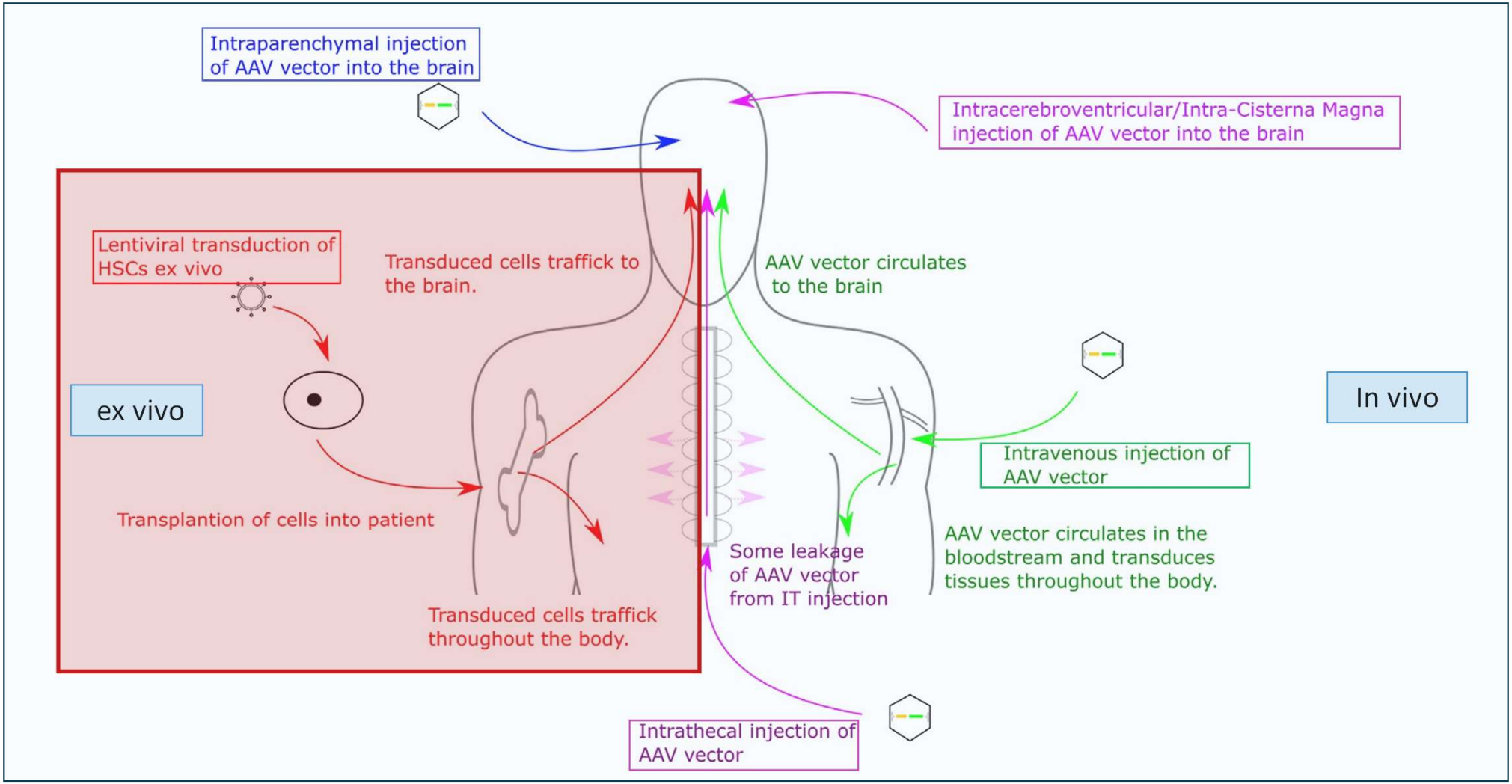


ex vivo

target cells can be removed from the body transfected with the molecular therapeutic and then provided back to the patient

Penon-Portmann M, Blair DR, Harmatz P. Current and new therapies for mucopolysaccharidoses. Pediatr Neonatol. 2023 Feb;64 Suppl 1:S10-S17.

Routes for gene therapy administration



Wood SR, Bigger BW. Delivering gene therapy for mucopolysaccharide diseases. Front Mol Biosci. 2022 Sep 12;9:965089

Advantages and disadvantages of gene therapy strategies

Gene therapy strategies	Advantages	Disadvantages
Retroviral vectors	• Incorporates gene of interest into host's genome for long-term correction • Use of a modified long terminal repeat can reduce the risk of insertional mutagenesis	• Possibility of insertional mutagenesis due to nontargeted incorporation into the genome • Ex vivo approaches may have a long waiting period in which disease progression can worsen the patient's condition • High dose of retroviral vector necessary for in vivo correction • Immune suppressant necessary for long-term expression in vivo • A modified LTR can reduce transduction rates to a point where their effectiveness is limited
Lentiviral vectors	• Nonreplicating • Stably integrate into genomes of many mammalian cell types	• Unable to establish long-term correction with single injection • Treatment of neonates may be necessary for long-term correction • Low transduction efficiency to HSPCs • Risks of insertional mutagenesis and immunogenicity
AAV vectors	• Lack viral DNA • Engineered to deliver DNA cargo through cell membrane • Nonreplicating • Able to target specific tissue types	• When targeting the liver, **hepatotoxicity is a possibility** • Short-term expression without gene editing • May require use of immunosuppressant • Possibility of inducing insertional mutagenesis related cancers • Possibility of inducing dorsal root ganglion pathologies • Concerns with cell specificity and necessary dose levels
Adenovirus	• Able to transduce replicating and nonreplicating cells. • Do not integrate into host genome without gene editing aids • Possible to target specific cell types with fiber modifications • Unconnected with germ-line mutagenesis	• Patient death in 1999 due to high dose and large immune response • Possibility of hepatotoxicity when liver- targeting
Gene editing	• Potential for permanent correction. • The targeting ability of CRIPSR allows for carefully designed changes to the genome	• Requires a method for delivery to cells • On- and off-target effects

Hurt SC, Dickson PI, Curiel DT. Mucopolysaccharidoses type I gene therapy. J Inherit Metab Dis. 2021 Sep;44(5):1088-1098.

Ongoing gene therapy trials (MPS I, II, IIIA, IIIB, and MPS VI)

Clinical trial identifier	Title	Status	Condition	Vector	Delivery	Sponsor	Phase
NCT03580083	RGX-111 Gene Therapy in Patients With MPS I	Ongoing	MPSI	AAV2/9	Intrathecal	Regenexbio	I/II
NCT03488394	Gene Therapy With Modified Autologous Hematopoietic Stem Cells for the Treatment of Patients With Mucopolysaccharidosis Type I, Hurler Variant (TigetT10_MPSIH)	Ongoing	MPSI	LV	HSCGT	IRCCS San Raffaele	I/II
NCT02702115	A Phase I/2, Multileft, Open-label, Single-dose, Dose-ranging Study to Assess the Safety and Tolerability of SB-318, a rAAV2/6-based Gene Transfer in Subjects With Mucopolysaccharidosis I (MPS I)	Ongoing	MPSI	AAV2/6 Zinc-Finger Nuclease	Intravenous	Sangamo Therapeutics	I/II
NCT02702115	Ascending Dose Study of Genome Editing by the Zinc Finger Nuclease (ZFN) Therapeutic SB-318 in Subjects With MPS I	Ongoing	MPSI	AAV2/6 Zinc-Finger Nuclease	Intravenous	Sangamo Therapeutics	I/II
NCT03566043	RGX-121 Gene Therapy in Patients With MPS II (Hunter Syndrome)	Ongoing	MPSII	AAV2/9	Intra-cerebroventricular	RegenexBio	I/II
NCT04571970	RGX-121 Gene Therapy in Children 5 Years of Age and Over With MPS II (Hunter Syndrome)	Ongoing	MPSII	AAV2/9	Intra-cerebroventricular	RegenexBio	I/II
NCT04597385	Long-term Follow-Up for RGX-121	Ongoing	MPSII	AAV2/9	Intra-cerebroventricular	RegenexBio	I/II
NCT00004454	Phase I/II Study of Retroviral-Mediated Transfer of Iduronate-2-Sulfatase Gene Into Lymphocytes of Patients With Mucopolysaccharidosis II (Mild Hunter Syndrome)	Completed	MPSII	Retrovirus	Intravenous injection of Lymphocytes	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)/ University of Minnesota	I/II
NCT03041324	A Phase I/2, Multileft, Open-label, Single-dose, Dose-ranging Study to Assess the Safety and Tolerability of SB-913, a rAAV2/6-based Gene Transfer in Subjects With Mucopolysaccharidosis II (MPS II)	Ongoing	MPSII	AAV2/6 Zinc-Finger Nuclease	Intravenous	Sangamo Therapeutics	I/II
NCT03041324	Ascending Dose Study of Genome Editing by the Zinc Finger Nuclease (ZFN) Therapeutic SB-913 in Subjects With MPS II	Terminated	MPSII	AAV2/6 Zinc-Finger Nuclease	Intravenous	Sangamo Therapeutics	I/II
NCT04628871	Long Term Follow-up (LTFU) of Subjects Who Received SB-318, SB-913, or SB-FIX (LTFU)	Ongoing	MPSI MPSII	AAV2/6 Zinc-Finger Nuclease	Intravenous	Sangamo Therapeutics	I/II
NCT01474343	Intracerebral Gene Therapy for Sanfilippo Type A Syndrome	Completed	MPSIIIA	AAVrh10	Intraparenchymal	Lysogene	I/II
NCT02053064	Long-term Follow-up of Sanfilippo Type A Patients Treated by Intracerebral SAF-301 Gene Therapy	Completed	MPSIIIA	AAVrh10	Intracranial	Lysogene	I/II
NCT03612869	Study of AAVrh10-h.SGSH Gene Therapy in Patients With Mucopolysaccharidosis Type IIIA (MPS IIIA) (AAVance)	Ongoing	MPSIIIA	AAVrh10	Intracranial	Lysogene	II/III
2015–000359–26	Phase I/II safety, tolerability and initial efficacy study of adeno-associated viral vector serotype 9 containing human sulfamidase gene after intracerebroventricular administration to patients with MPSIIIA.	Ongoing	MPSIIIA	AAV2/9	Intra-cerebroventricular	Laboratorios del Dr. Esteve, S.A.	I/II
NCT02716246	Phase I/II Gene Transfer Clinical Trial of scAAV9.U1a.hSGSH for Mucopolysaccharidosis (MPS) IIIA	Ongoing	MPSIIIA	AAV2/9	Intravenous	Abeona Therapeutics (ABO-102 now with Ultragenyx)	I/II
NCT04088734	A Phase I/II Open Label, Single-dose, Gene Transfer Study of scAAV9.U1a.hSGSH (ABO-102) in Patients With Middle and Advanced Phases of MPS IIIA Disease	Terminated	MPSIIIA	AAV2/9	Intravenous	Abeona Therapeutics	I/II
NCT04360265	A Long-term Follow-up Study of Patients With MPS IIIA Treated With ABO-102	Ongoing	MPSIIIA	AAV2/9	Intravenous	Abeona Therapeutics	I/II
NCT04201405	Gene Therapy With Modified Autologous Hematopoietic Stem Cells for Patients With Mucopolysaccharidosis Type IIIA	Ongoing	MPSIIIA	LV	HSCGT	Orchard Therapeutics/ University of Manchester	I/II
NCT03300453	Intracerebral Gene Therapy in Children With Sanfilippo Type B Syndrome	Completed	MPSIIIB	AAV2/5	Intraparenchymal	Institut Pasteur/UniQure Biopharma B.V.	I/II
NCT03315182	Gene Transfer Clinical Trial for Mucopolysaccharidosis (MPS) IIIB (MPSIIIB)	Terminated	MPSIIIB	AAV2/9	Intravenous	Abeona Therapeutics	I/II
NCT04655911	A Long-term Follow-up Study of Patients With MPS IIIB Treated With ABO-101	Ongoing	MPSIIIB	AAV2/9	Intravenous	Abeona Therapeutics	I/II
NCT03173521	Gene Therapy in Patients With Mucopolysaccharidosis Disease	Ongoing	MPSVI	AAV2/8	Intravenous	Fondazione Telethon	I/II

Wood SR, Bigger BW. Delivering gene therapy for mucopolysaccharide diseases. Front Mol Biosci. 2022 Sep 12;9:965089.

Ongoing gene therapy trials (MPS I, II, IIIA, IIIB, and MPS VI)

Clinical trial identifier	Title	Status	Condition	Vector	Delivery	Sponsor	Phase
NCT03580083	RGX-111 Gene Therapy in Patients With MPS I	Ongoing	MPSI	AAV2/9	Intrathecal	Regenexbio	I/II
NCT03488394	Gene Therapy With Modified Autologous Hematopoietic Stem Cells for the Treatment of Patients With Mucopolysaccharidosis Type I, Hurler Variant (TigetT10_MPSIH)	Ongoing	MPSI	LV	HSCGT	IRCCS San Raffaele	I/II
NCT02702115	A Phase I/2, Multileft, Open-label, Single-dose, Dose-ranging Study to Assess the Safety and Tolerability of SB-318, a rAAV2/6-based Gene Transfer in Subjects With Mucopolysaccharidosis I (MPS I)	Ongoing	MPSI	AAV2/6 Zinc-Finger Nuclease	Intravenous	Sangamo Therapeutics	I/II
NCT02702115	Ascending Dose Study of Genome Editing by the Zinc Finger Nuclease (ZFN) Therapeutic SB-318 in Subjects With MPS I	Ongoing	MPSI	AAV2/6 Zinc-Finger Nuclease	Intravenous		
NCT03566043	RGX-121 Gene Therapy in Patients With MPS II (Hunter Syndrome)	Ongoing	MPSII	AAV2/9	Intra-cerebroventricular		
NCT04571970	RGX-121 Gene Therapy in Children 5 Years of Age and Over With MPS II (Hunter Syndrome)	Ongoing	MPSII	AAV2/9	Intra-cerebroventricular		
NCT04597385	Long-term Follow-Up for RGX-121	Ongoing	MPSII	AAV2/9	Intra-cerebroventricular		
NCT00004454	Phase I/II Study of Retroviral-Mediated Transfer of Iduronate-2-Sulfatase Gene Into Lymphocytes of Patients With Mucopolysaccharidosis II (Mild Hunter Syndrome)	Completed	MPSII	Retrovirus	Intravenous injection of Lymphocytes	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)/ University of Minnesota	I/II
NCT03041324	A Phase I/2, Multileft, Open-label, Single-dose, Dose-ranging Study to Assess the Safety and Tolerability of SB-913, a rAAV2/6-based Gene Transfer in Subjects With Mucopolysaccharidosis II (MPS II)	Ongoing	MPSII	AAV2/6 Zinc-Finger Nuclease	Intravenous	Sangamo Therapeutics	I/II
NCT03041324	Ascending Dose Study of Genome Editing by the Zinc Finger Nuclease (ZFN) Therapeutic SB-913 in Subjects With MPS II	Terminated	MPSII	AAV2/6 Zinc-Finger Nuclease	Intravenous	Sangamo Therapeutics	I/II
NCT04628871	Long Term Follow-up (LTFU) of Subjects Who Received SB-318, SB-913, or SB-FIX (LTFU)	Ongoing	MPSI MPSII	AAV2/6 Zinc-Finger Nuclease	Intravenous	Sangamo Therapeutics	I/II
NCT01474343	Intracerebral Gene Therapy for Sanfilippo Type A Syndrome	Completed	MPSIIIA	AAVrh10	Intraparenchymal	Lysogene	I/II

5 MPS I (1 ex vivo, 4 in vivo)
8 MPS II (all in vivo)
7 MPS IIIA (1 ex vivo, 6 in vivo)
4 MPS IIIB (all in vivo)

Clinical trial identifier	Title	Status	Condition	Vector	Delivery	Sponsor	Phase
NCT02053064	Long-term Follow-up of Sanfilippo Type A Patients Treated by Intracerebral SAF-301 Gene Therapy	Completed	MPSIIIA	AAVrh10	Intracranial	Lysogene	I/II
NCT03612869	Study of AAVrh10-h.SGSH Gene Therapy in Patients With Mucopolysaccharidosis Type IIIA (MPS IIIA) (AAVance)	Ongoing	MPSIIIA	AAVrh10	Intracranial	Lysogene	II/III
2015-000359-26	Phase I/II safety, tolerability and initial efficacy study of adeno-associated viral vector serotype 9 containing human sulfamidase gene after intracerebroventricular ients with	Ongoing	MPSIIIA	AAV2/9	Intra-cerebroventricular	Laboratorios del Dr. Esteve, S.A.	I/II
	sfer Clinical hSGSH for is (MPS) IIIA	Ongoing	MPSIIIA	AAV2/9	Intravenous	Abeona Therapeutics (ABO-102 now with Ultragenyx)	I/II
	el, Single-dose, of (ABO-102) in and Advanced Phases of MPS IIIA Disease	Terminated	MPSIIIA	AAV2/9	Intravenous	Abeona Therapeutics	I/II
NCT04360265	A Long-term Follow-up Study of Patients With MPS IIIA Treated With ABO-102	Ongoing	MPSIIIA	AAV2/9	Intravenous	Abeona Therapeutics	I/II
NCT04201405	Gene Therapy With Modified Autologous Hematopoietic Stem Cells for Patients With Mucopolysaccharidosis Type IIIA	Ongoing	MPSIIIA	LV	HSCGT	Orchard Therapeutics/ University of Manchester	I/II
NCT03300453	Intracerebral Gene Therapy in Children With Sanfilippo Type B Syndrome	Completed	MPSIIIB	AAV2/5	Intraparenchymal	Institut Pasteur/UniQure Biopharma B.V.	I/II
NCT03315182	Gene Transfer Clinical Trial for Mucopolysaccharidosis (MPS) IIIB (MPSIIIB)	Terminated	MPSIIIB	AAV2/9	Intravenous	Abeona Therapeutics	I/II
NCT04655911	A Long-term Follow-up Study of Patients With MPS IIIB Treated With ABO-101	Ongoing	MPSIIIB	AAV2/9	Intravenous	Abeona Therapeutics	I/II
NCT03173521	Gene Therapy in Patients With Mucopolysaccharidosis Disease	Ongoing	MPSVI	AAV2/8	Intravenous	Fondazione Telethon	I/II

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Example for gene therapy trials in MPS I

- two ongoing phase I/II GT trials:

Ex vivo

- OTL-203 by Orchard Therapeutics
- autologous hematopoietic stem cell approach
- lentiviral vector encoding the a-L-iduronidase (IDUA) gene
- 8 patients with MPS IH received after myeloablative conditioning
- Interim results showed a safety profile like autologous HSCT:
  - all patients showed prompt, sustained engraftment and supraphysiological blood and CSF IDUA levels
  - urine and CSF GAGs decreased appropriately
  - patients showed stable neurocognitive performance with ongoing motor development

In vivo

- RGX-111 by REGENEXBIO
- a copy of a-L-iduronidase (IDUA) gene packaged into an AAV-9 vector administered directly into the CNS
- The trial's endpoints are safety, biomarker reduction, and improvements in neurodevelopment
- 5 patients have been successfully dosed
- no serious drug-related adverse events
  - Biomarker and neuro- developmental assessments also indicate an encouraging CNS response

- no drug-related serious adverse events
- reduction in CNS-relevant biomarkers
- improvement in caregiver reported outcomes
- positive trends in neurodevelopment.

Penon-Portmann M, Blair DR, Harmatz P. Current and new therapies for mucopolysaccharidoses. Pediatr Neonatol. 2023 Feb;64 Suppl 1:S10-S17.

Pros and cons of gene therapy

pros	cons
• Permanent approach	increasing the risk for genotoxicity
• no drug-related serious AEs	Vector needs to pass several structures and need to promote high gene expression
• reduction in CNS-relevant biomarkers	Difficulties due to attacks of the immune system
• improvement in caregiver reported outcomes	High costs
• positive trends in neurodevelopment	

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Other treatments

Anti-inflammatory therapy

- e.g. Adalimumab (TNFα inhibitor) immunmodulator on skeletal disease
  => placebo-controlled double blind study in MPS I, II and VI
  => pilot study showed improvement in physical function and pain

Substrate reduction therapy

- e.g. genistein- no effect in clinical trials (MPS III)

Oral GAG clearance

- e.g. Odiparcil

$\Rightarrow$ odiparcil effectively diverts the synthesis of cellular glycosaminoglycans into secreted soluble species

$\Rightarrow$ Phase I/II in MPS VI

Subcutaneous GAG clearance

S.c. GAG clearance

Pentosan Polysulphate (PPS)

$\Rightarrow$ Single center study in adult MPS I patients (reduced pain, improvements in joint range of motion)

Fetal therapies

- e.g. intrauterine enzyme replacement therapy

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Entchev E, Jantzen I, Masson P, Bocart S, Bournique B, Luccarini JM, Bouchot A, Lacombe O, Junien JL, Broqua P, Tallandier M. Odiparcil, a potential glycosaminoglycans clearance therapy in mucopolysaccharidosis VI-Evidence from in vitro and in vivo models. PLoS One. 2020 May 15;15(5):e0233032.

Thank you for your attention!!

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