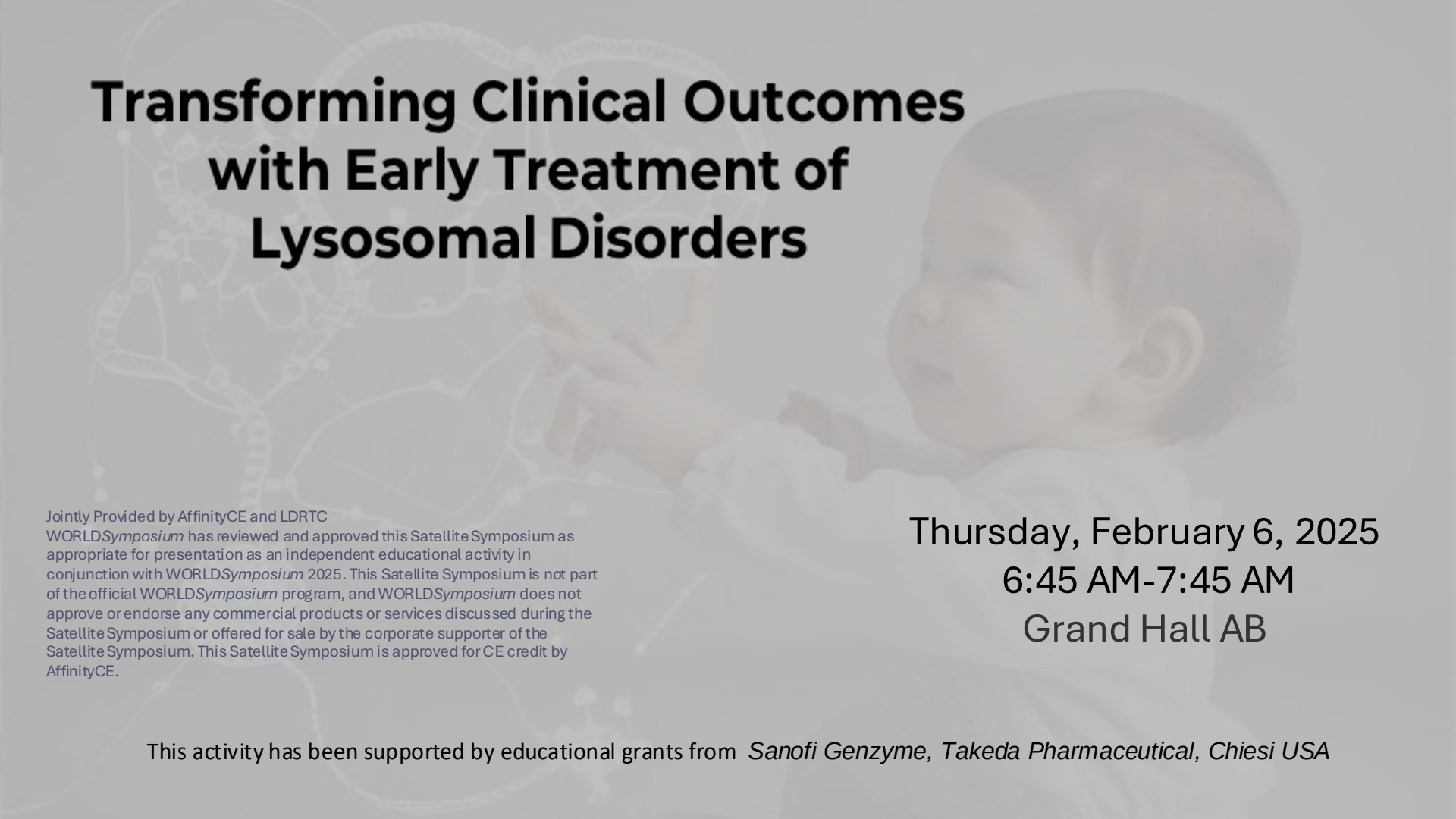
Transforming Clinical Outcomes with Early Treatment of Lysosomal Disorders



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Thursday, February 6, 2025
6:45 AM-7:45 AM
Grand Hall AB

This activity has been supported by educational grants from *Sanofi Genzyme, Takeda Pharmaceutical, Chiesi USA*

Why Early Treatment for Lysosomal Disorders Matters?

- **Pathophysiology and the "Point of No Return"**
  - A critical "point of no return" occurs when pathological changes (e.g., neuronal death, fibrosis) become irreversible, even if substrate levels are corrected later.
  - Organ systems with limited regenerative capacity, such as the central nervous system (CNS), are particularly vulnerable.
- **Reversibility and Early Intervention**
  - Once structural or functional damage is established, therapy may only slow progression rather than restore normal function.
- **Higher Disease Load, Shorter Disease Duration**.
  - A short disease duration at diagnosis enables better outcomes since fewer irreversible changes have occurred.

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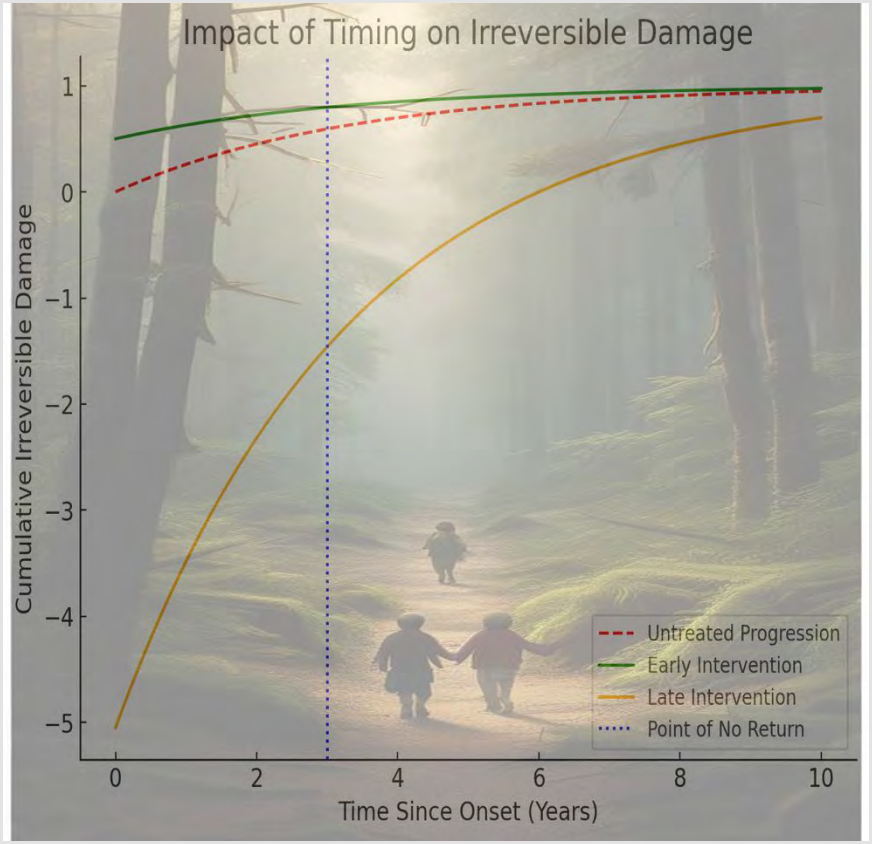


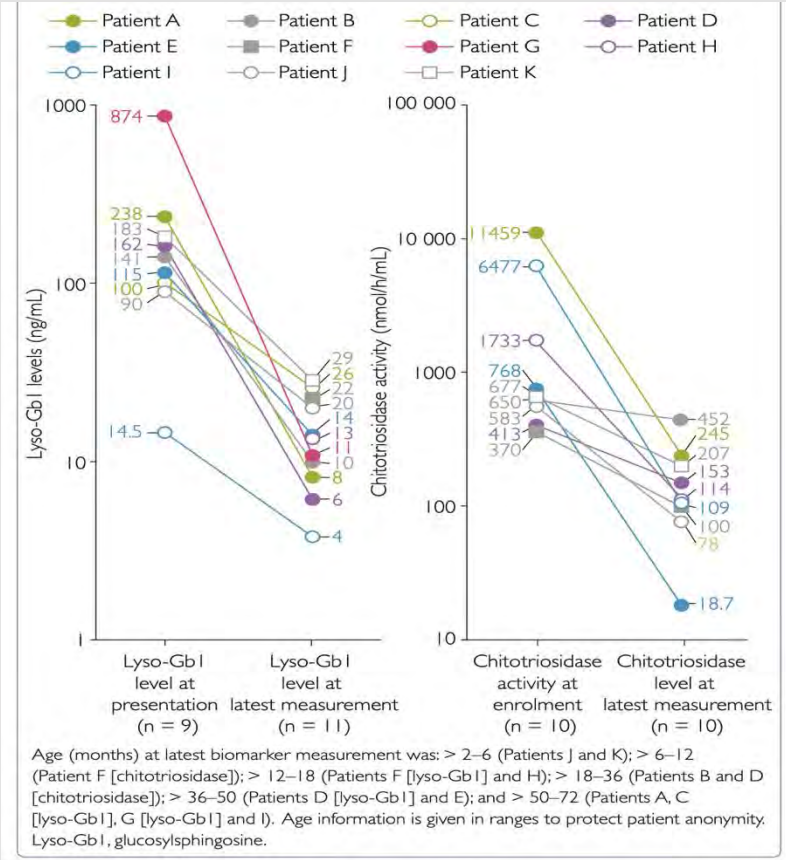
Treatment of Infants and Young Children with Gaucher Disease

LysoGb1 is released into the circulation from dead/dying or dysfunctional cells/tissues and macrophages

Lyso-Gb1 is a deacetylated form of glucosylceramide formed via a metabolic pathway that is significantly active only in the absence of GCase

The highest levels (200-400 fold elevations) were observed in untreated GD2 and GD3 patients. (presenter's own data)

- Newborn, L444(483)P/Rec Δ55,
- 3-year-old with wide-based gait, R463(R502)C/Rec
- 55-year-old with a history of lymphoma, extensive marrow replacement, and severe HSM, N370 (409)S/Rec Δ55,



Goker-Alpan et al, manuscript submitted

Faculty and Disclosures

Moderator

Dr. Goker-Alpan is on the Advisory Board/Consultant for Chiesi, Takeda, Sanofi, Prevail/Lilly, Sparks Therapeutics, Uniqure, Astellas, Spur, and Team Sanfilippo. She receives grants/research support from Chiesi, Sanofi, Takeda, Prevail/Lilly, Spark Therapeutics, Amicus, Spur/Freeline, Sangamo, Cyclo, Indorsia, 4DMT, Homology. She is on the speaker bureau for Sanofi, Takeda, Amicus, Chiesi, IntraBio.

Dr. Kronn is on Sanofi's Advisory Board and speaker bureau and receives research funding from Sanofi.

Dr. Jalazo is on the Advisory Board for Sanofi and Ionis.

Dr. Ramaswami is on the Advisory Board for Amicus, Chiesi, Sanofi, and Takeda. She receives research grants from Chiesi and Intrabio.

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Lindsay Torrice has no relevant financial relationships with ineligible companies to disclose.

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Pompe Disease: Early Treatment Paradigms in Pompe Disease: Lessons and Advances

David F. Kronn, MD, FACMG
New York Medical College

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Introduction

- The Spectrum of Pompe Disease
- Advances in Early Diagnosis: Newborn Screening
- Outcome of Early Treatment of Infantile Onset Pompe Disease
- Lessons Learned

Milestones in Pompe Disease

- 1932 First Description of Pompe Disease by Johannes Pompe, Dutch Pathologist
- 1963 The Belgian biochemist Henri-Gery Hers discovered the maltase (GAA) enzyme
- 1991 Cloning of GAA gene
- 2006 FDA Approval of Aglucosidase Alpha for treatment of IOPD and LOPD
- 2005 - 2007 Pilot Newborn Screening Program in Taiwan
- 2014 Newborn Screening for Pompe Disease started in New York State
- 2015 Newborn Screening for Pompe Disease added to the RUSP
- 2021 Approval of Avalglucosidase Alpha by FDA for treatment of LOPD in patients over one year of age
- 2023 Cipaglucosidase Alpha approved by FDA for treatment of LOPD

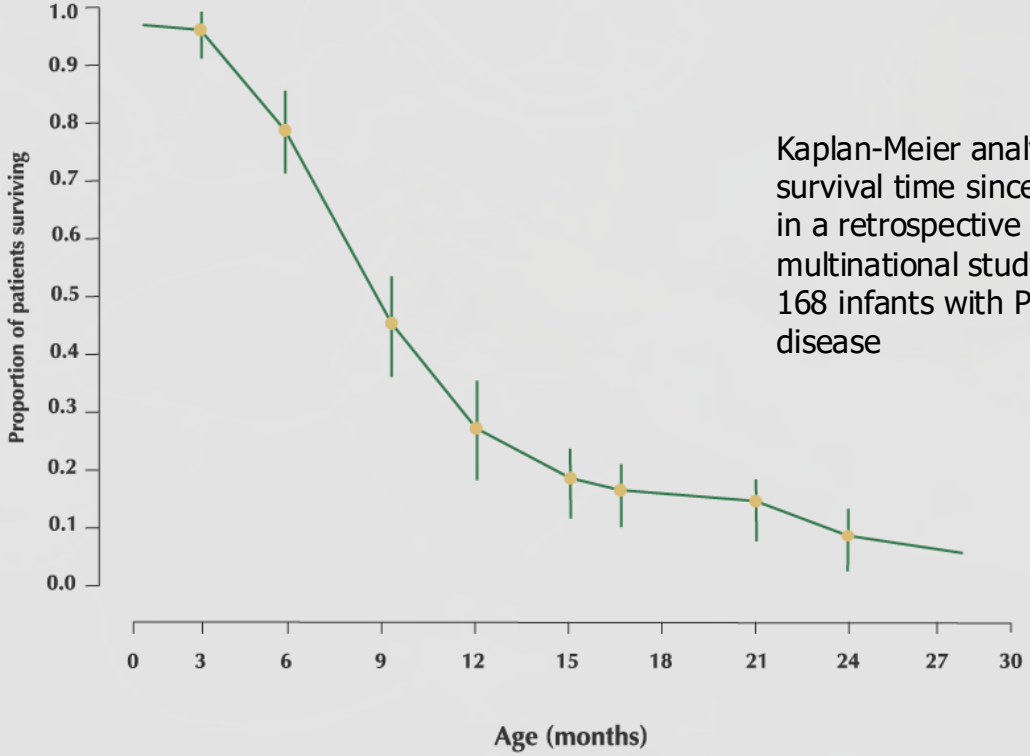
Pompe Disease Overview

- Characterized by the absence or marked deficiency of a lysosomal enzyme, acid alpha-glucosidase (GAA)
- Results in intralysosomal accumulation of glycogen in numerous tissues and cell types, primarily muscle cells
- Often leads to progressive debilitation, organ failure, and/or death
- Recognizing Pompe disease can be challenging as signs and symptoms may be shared with other disorders
- Early diagnosis and treatment are critical to optimizing outcomes

Continuum of Clinical Phenotypes

- Single-disease continuum
- Variable age of onset and extent of organ involvement
- Variable rates of disease progression
- Essential to recognize presentation
- Disease is progressive in all cases
- Early diagnosis is very important

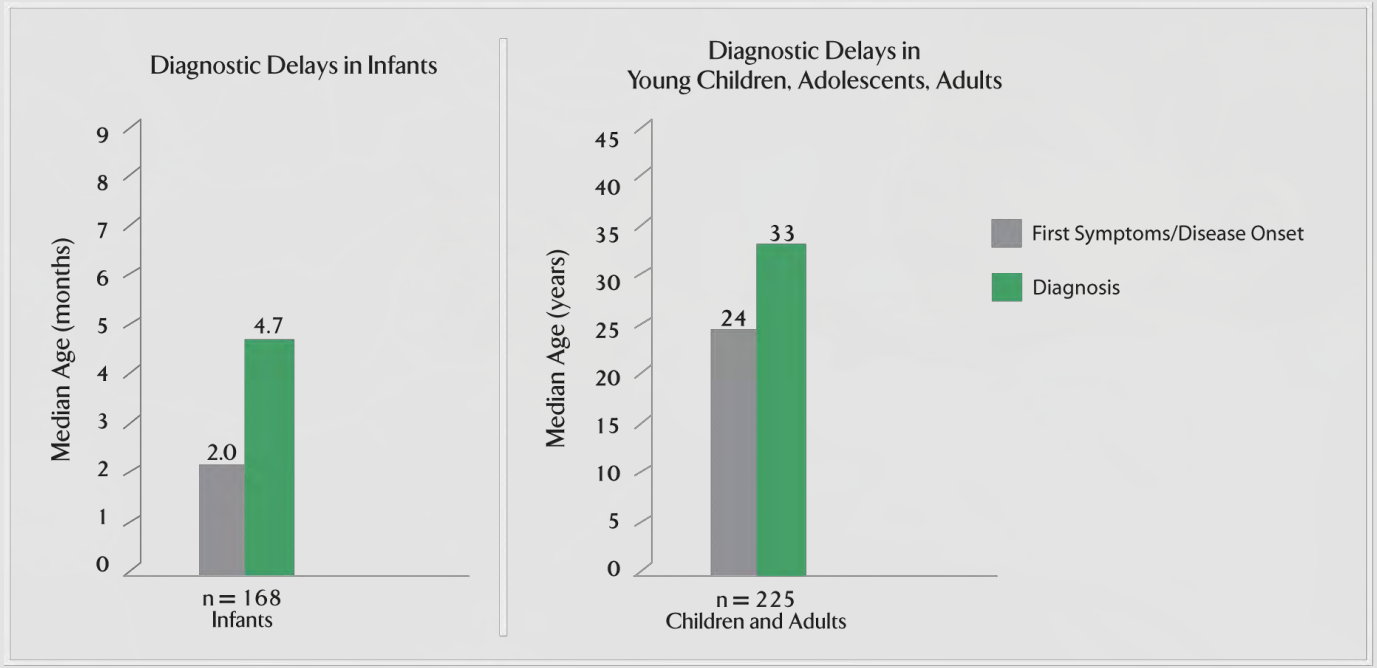
Survival of Infants with Pompe Disease Prior to 2006



Kaplan-Meier analysis of survival time since birth in a retrospective multinational study of 168 infants with Pompe disease

Reprinted from Kishnani et al. J Pediatr 2006; 148:671-6, with permission from Elsevier.

Diagnostic Delays Were Common



Kishnani et al. J Pediatr 2006; 148:671-6

Winkel et al. J Neurol 2005; 252:875-84

What is Pompe Disease?

- GAA Deficiency
- Biallelic Pathological GAA Variants
- Clinical Manifestations
- Biomarker elevation

Classification of Pompe Disease in the Age of Newborn Screening

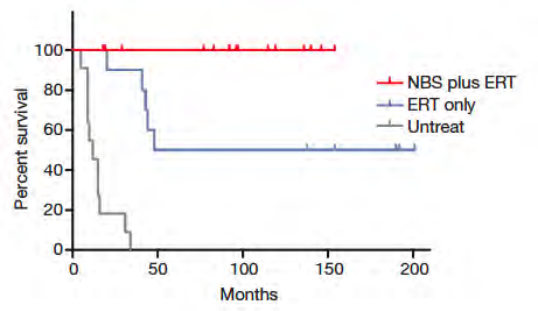
- Infantile Onset Pompe Disease (IOPD)
- Late Onset Pompe Disease (LOPD)
- Variant IPOD/LOPD
- At Risk for LOPD

Newborn Screening for Pompe Disease

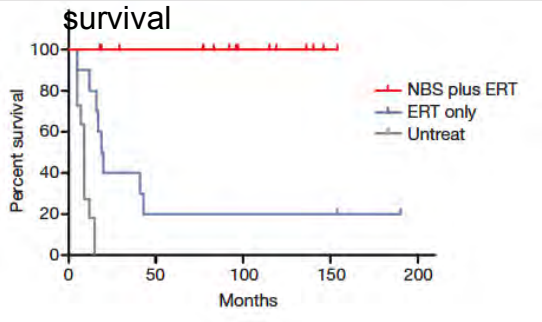
- Blood spot analysis of GAA activity
- Taiwan Experience: 10/1/05 – 12/31/07
  - 6 confirmed cases from 206,088 birth (45% of pop.)
  - All treated early with myozyme, all surviving walking. Cardiac involvement noted on all patients at birth
  - Clinical comparators faired worse, pt's diagnosed later than 6 month died or became vent dependent. Earlier diagnosed patients had significant developmental delays.
  - All cases CRIM +ve
- Approved by RUSP in 2015
- Methods for screening vary between States, and few offer molecular second tier testing
- Incidence of IOPD between 1:100,000 and 1:200,000
- Incidence of patients at risk for LOPD higher than previously expected
- Overall incidence of Pompe Disease around 1:20,000

Taiwan Pompe Disease Experience: NBS and Early ERT Initiation Significantly Improved Outcomes

Overall survival



Invasive ventilator-free survival



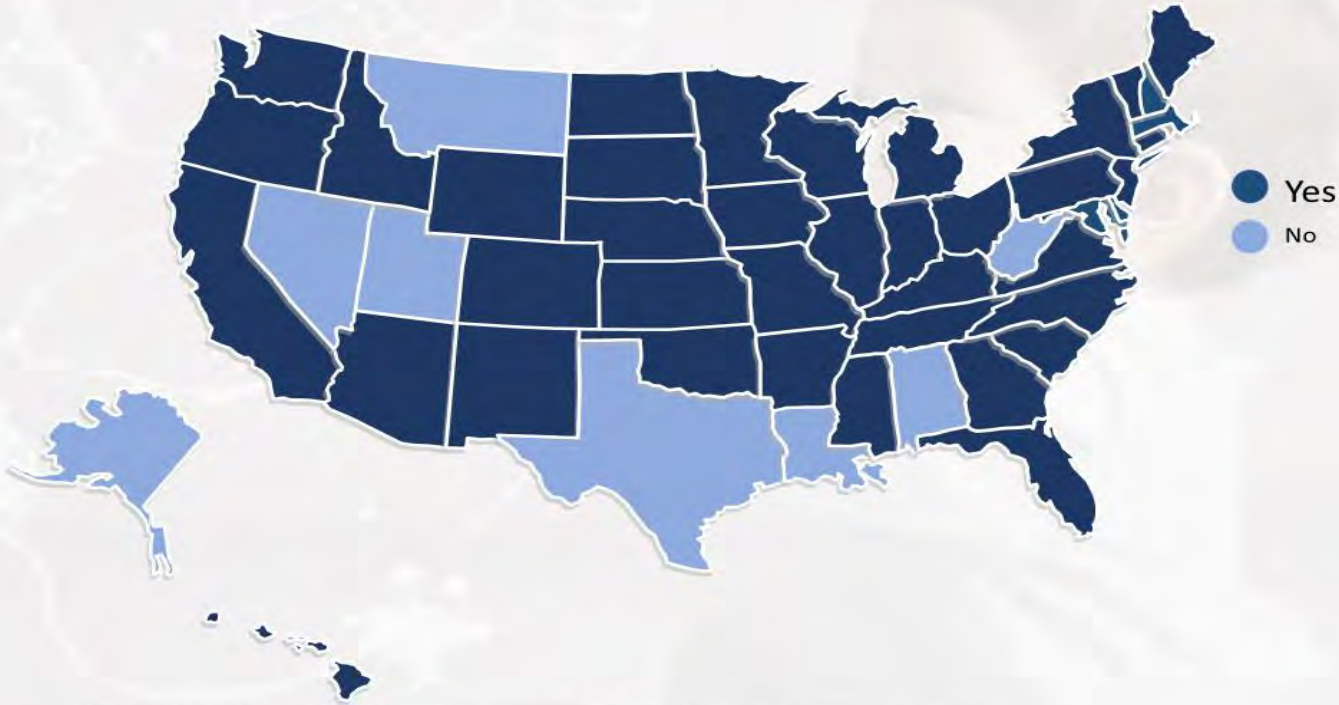
NBS plus ERT: 5 patients confirmed IOPD at age 7 to 33 days received ERT 1 to 7 days after diagnosis

ERT only: 10 patients symptomatic upon IOPD diagnosis received first ERT at age 2 to 6 months

- Survival was 100% in patients identified by NBS who received early ERT
- Poor prognosis demonstrated in patients who start ERT after symptoms develop

ERT, enzyme replacement therapy; IOPD, infantile-onset Pompe disease; NBS, newborn screening.
Reference: Chien YS et al. *Ann Tranl Med.* 2019;7(13):281.

Newer RUSP Diseases: Pompe Disease 2025



Conditions screened by state. Baby's First Test (as of 1/21/2025). https://babysfirsttest.org/newborn-screening/states.

Management of Patient's Diagnosed with or at Risk for Pompe Disease Following an Abnormal NBS

- Evidence of Cardiomyopathy
- Confirmatory Enzyme Assay
- Molecular Diagnostics
- CRIM Status – Erasmus Database
- Dx – IOPD, Treatment Decisions
  - Agree to start treatment
  - Immunomodulation – Full or Modified
- Dx – At Risk for LOPD
  - Follow up
  - Stable or Showing signs of clinical progression – CPK, Hex4, Developmental Milestone, PT Evaluation

Initial Management Decisions in Pompe Disease

- IOPD
  - Classic disease vs atypical
  - CRIM status: positive vs negative
  - Should the patient receive immunomodulation?
  - Which immunomodulation protocol?
  - Starting dose and frequency of ERT
  - Should new treatment options be considered?
- LOPD
  - When should treatment be initiated?
  - Should modified immunomodulation be used?
  - Starting dose and frequency of ERT
  - Should new treatment options be considered?

CRIM, cross-reactive immunologic material; ERT, enzyme replacement therapy; IOPD, infantile-onset Pompe disease; LOPD, late-onset Pompe disease.
Reference: Kronn DF et al. *Pediatrics*. 2017;140(S1):S24-S45.

ERT in CRIM –ve Patients

- Develop high levels of anti-rhGAA antibodies, and ultimately fatal
- Induction of immune modulation
- Case History
  - 5 wk African American , homozygous for R854 stop mutation, no GAA detected on Western Blot
  - Rapid rise in IgG antibodies 1:1600
  - Immune Modulation Regimen
    - Rituximab 375 mg/m², weekly then every 4 t 12 weeks
    - Methotrexate 0.5 mg per kg after seven weekly, given weekly
    - IVIG 500mg/kg every 4 weeks
  - On going clinic benefit in patient
- May be beneficial in replacement protein elicits robust antibody responses

IOPD Patient's Followed Since NBS Started in New York State in April 2014

Patient	NBS	Current Age (yrs)	Cardiomyopathy at birth	Crim Status	Immunomodulation	Ventilator Support	Hearing Loss	Speech Delay	Glasses	Devel. Delay	Other Issues
JC	Yes	4	No- developed by 2 months of age	Positive	Yes-MTX	No	Not tested	Yes	No	No	SGA
SF	Yes	10	Yes	Positive	Yes-MTX	No	Yes	Yes	Yes	Yes	Tall / FTT
MK	Yes	6	Yes	Negative	Yes-MTX /Rituximab/IVIG	Yes-BiPap at Night	Yes	Yes	Yes	Yes	Scoliosis/Kyphosis Hypothyroidism s/p thyroidectomy
MK	Yes	8	No - Developed by six wks of age	Positive	Yes-MTX	No	Yes	Hypernasal	No	No	Asthma, School behavior issues.
MC	Yes	6	No	Positive	Yes-MTX	No	Not tested	No	No	No	None
MP	Yes	7	Yes	Positive	Yes-MTX	No	Yes	Yes	No	Yes	Tall / FTT
EP	No	9	Yes	Positive	Yes - MTX/Rituximab/IVIG	No	Yes	Hypernasal	Yes	No	Hyperflexible joints
RW	Yes	5	Yes	Positive	Yes-MTX	No	Not tested	Yes	No	Yes	ADHD

Management of Patient's at Risk for LOPD

- After initial diagnosis, follow up at 1 month – patients with splice site variant do not have cardiomyopathy
- Follow up at 3 months
- Sequential monitoring of CPK and Hex4
- Follow up at 6, 9 and 12 months if stable, then less frequently
- Patients with rising biomarkers need closer follow up
- Consider starting ERT if evidence of disease progression
- On Going monitoring

When to Start ERT in Previously Asymptomatic Patients?

- Continually rising biomarkers
- Any evidence of muscle weakness on sequential exam
- Failure to meet milestones
- Worsening PT evaluation
- Abnormal PFT's

- If abnormalities present follow up patient at shorter interval with discussion about starting ERT with parents
    - Have to weight disease burden with treatment burden

Ongoing Management of Asypmtomatic Patients at Risk for LOPD

- After year one
  - Following every six months with CPK and Hex4
  - If no change in biomarkers considers follow up annually with CPK and Hex4 every 6 months
  - Any concerns shorten interval of visits
  - Ideally have a baseline Physical therapy evaluation
  - Need buy in from parents to maintain follow up
- After year five
  - Continue interval evaluations
  - Baseline Pulmonary Functions Tests

Lessons Learned

- What did we know?
  - Previously Pompe Disease was divided into IOPD and LOPD
  - No effective treatment prior to ERT introduction in 2006
  - Outcomes of IOPD suboptimal with clinical diagnosis
  - LOPD with long delays in diagnosis after onset of symptoms

- What have we learned?
  - Pompe Disease is very heterogeneous even within IOPD there are variations in presentation, not all newborns have cardiomyopathy at the time of their initial newborn screening referral.
  - Only a few patient's have clear genotype phenotype correlations
  - Benefit of early treated IOPD after NBS diagnosis

- On Going Questions?
  - New treatments needed to prevent disease progression in IOPD and LOPD
  - What is the Long Term outcome of NBS diagnosed LOPD?

Pompe Disease Clinical Spectrum

Though 2 major forms have been described, Pompe disease presents as a broad, continuous spectrum of clinical phenotypes [1-4]

Infantile-onset Pompe disease (IOPD)

- Absent or very low (<1%) GAA activity
- Symptomatic before 1 year of age, usually within the first few months
- All patients have cardiomyopathy
- Other common symptoms include hypotonia, muscle weakness, failure to thrive, and respiratory infections or dyspnea leading to respiratory failure
- Typically fatal within 1 year of life without treatment

Patients may present with a wide variety of…

Genotypes
Phenotypes
GAA activity
Age of diagnosis
Age of symptom onset
Muscle and cardiac involvement
Organ involvement
Wheelchair or ventilator dependency

…that defy strict classification in 1 of 2 categories

Late-onset Pompe disease (LOPD)

- Low or moderately-low (2% to 40%) GAA activity
- Symptomatic anytime after 1 year of age through adulthood or ≤1 year without cardiomyopathy
- Disease tends progress more rapidly and be more severe with earlier onset of symptoms and male sex
- Most patients do not have cardiomyopathy
- Progressive muscle weakness results in wheelchair dependency, respirator need, and/or shortened life expectancy

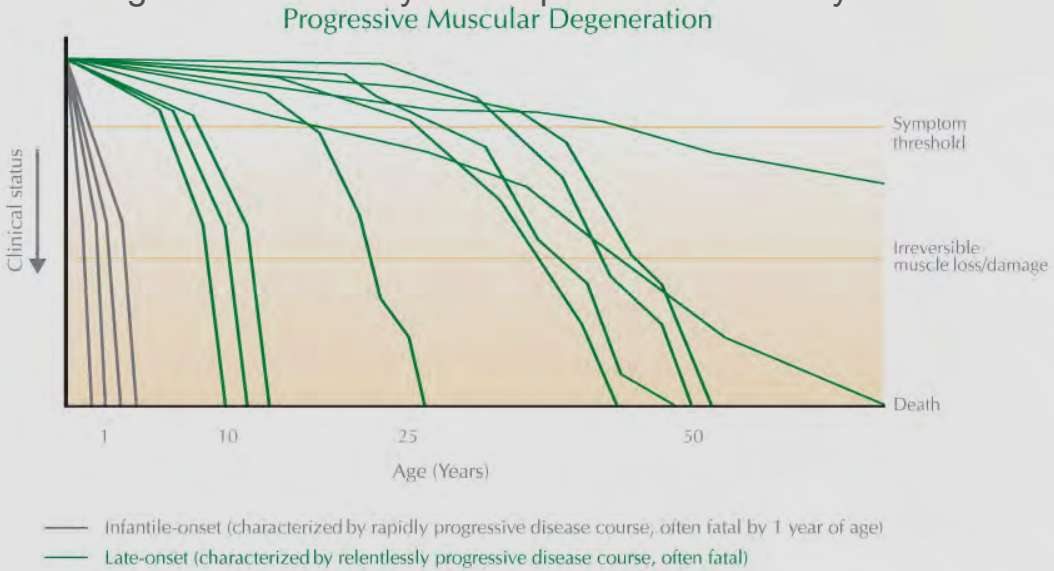
GAA, acid α-glucosidase

References: 1. van Capelle CI, et al. *Orphanet J Rare Dis*. 2016;11(1):65. **2.** Morales JA and Anilkumar AC. Glycogen Storage Disease Type II (Pompe Disease). *NCBI StatPearls*. StatPearls Publishing; 2020-. Accessed March 14, 2020. https://www.ncbi.nlm.nih.gov/books/NBK470558/. **3.** Kronn DF et al. *Pediatrics*. 2017;140(S1):S24-S45. **4.** Burton BK, et al. *Pediatrics*. 2017;140(Suppl 1):S14-S23.

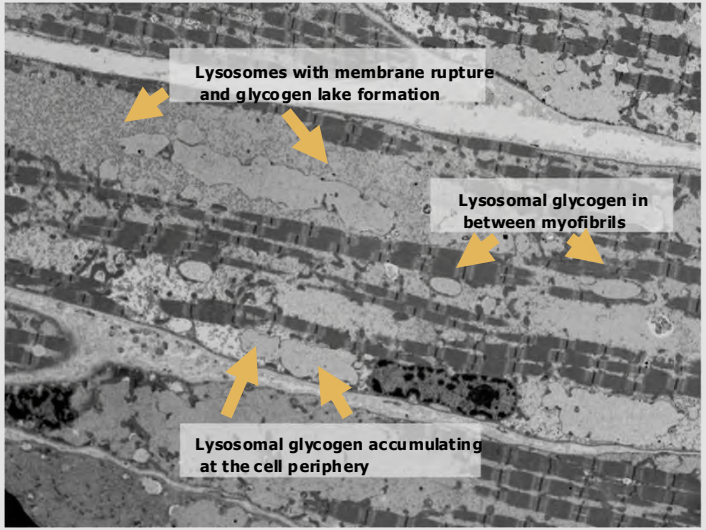
Pompe Disease Overview

Wide Range of Phenotypes

- Ranges from a rapidly progressive disease course (usually fatal by 1 year of age) to a variable and relentlessly progressive course with significant morbidity and/or premature mortality



Pathogenesis



Electron microscopy in skeletal muscle of infantile patient. Magnification 6500x. Image courtesy of Genzyme Pathology.

- Healthy myofibrils are replaced by glycogen, gradually impairing muscle function[1]
- Muscle pathology may precede symptomatology
- Glycogen accumulation begins before signs of clinical weakness, so early muscle damage may not be clinically detectable

1. Hesselink RP, et al. Biochim Biophys Acta 2003; 1637:164-70.

Newborn Screening for Pompe Disease

- Blood spot analysis of GAA activity
- Taiwan Experience: 10/1/05 – 12/31/07
  - 6 confirmed cases from 206,088 birth (45% of pop.)
  - All treated early with myozyme, all surviving walking. Cardiac involvement noted on all patients at birth
  - Clinical comparators faired worse, pt's diagnosed later than 6 month died or became vent dependant. Earlier diagnosed patients had significant developmental delays.
  - All cases CRIM +ve

Asymptomatic Patients at Risk for LOPD – Points to Consider

- If patients remain asymptomatic discuss plan with parents for follow up
  - Consider partnering with the patients pediatrician
- Be clear about patient's diagnostic finding and the risk for progression with the parents
  - Need buy in to prevent loss to follow up
- If a patient is showing clear signs and symptoms of disease progression don't watch and wait
  - ERT works better at slowing disease progression

MPS 1 and MPS 2
Optimizing Outcomes in MPS 1 and MPS 2: The Role of Early Diagnosis and Therapy

Elizabeth Jalazo, MD, University of North Carolina
Chapel Hill, North Carolina, USA

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Learning Objectives:

After this activity, participants will be able to:

1. Identify common presenting symptoms of MPS I and MPS II
2. Recognize the spectrum of clinical manifestations associated with these disorders
3. Identify limitations of current enzyme replacement therapy (ERT) approaches

MPS I, Hurler-Scheie Spectrum

Progressive multisystem disorder resulting from loss of alpha-iduronidase enzyme, with features ranging over a continuum of severity. While affected individuals have traditionally been classified as having one of 3 MPS I syndrome (Hurler, Hurler-Scheie or Scheie syndrome) the clinical features overlap and distinguishing and predicting phenotype biochemically is challenging.

Clarke LA. Mucopolysaccharidosis Type I. 2002 Oct 31 [Updated 2021 Feb 25] GeneReviews®

**significant portion of individuals with attenuated MPS I have later-onset cognitive decline. Individuals with attenuated phenotype age 2-6yo had normal IQ scores, 43% of patients in 6-25yo group had either borderline or impaired cognition*

Kubaski, 2020

Allogeneic HSCT is the gold standard treatment for severe MPS I, Hurler syndrome

HSCT can alleviate several disease symptoms and improves survival with best outcomes when 1) performed before age of 2 years old and 2) prior to evidence of cognitive impairment (DQ >80-85)

Additionally, HSCT reduces facial coarseness, joint mobility and improves sleep apnea, cardiac disease and hearing loss

Overall, survival is significantly improved with HSCT and when initiated early can stabilize neurocognitive decline

Shapiro E.G. et al. 2015

Earlier transplant results in improved neurological outcome

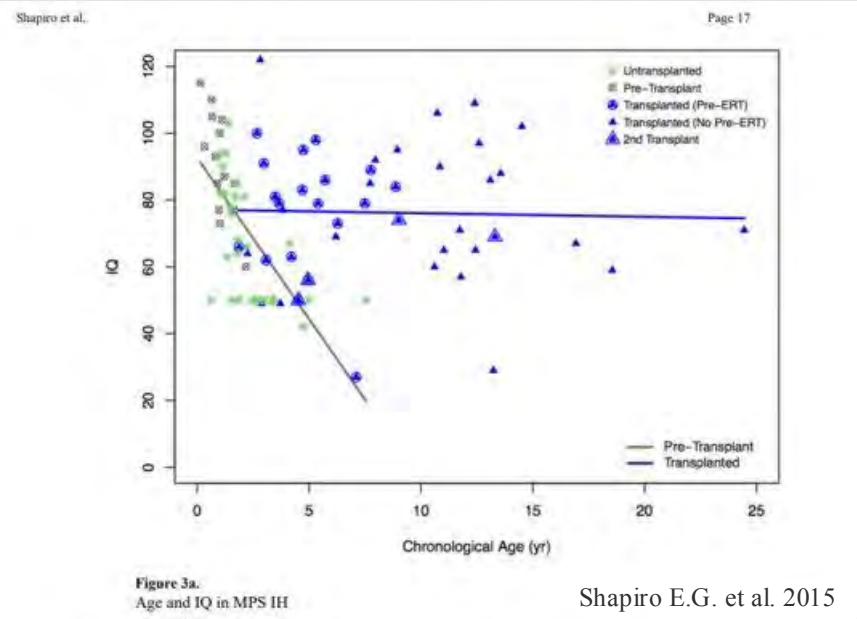


Figure 3a.
Age and IQ in MPS IH

Shapiro E.G. et al. 2015

Table 1

Effect of HSCT and ERT on clinical manifestations in MPS I.

Clinical Manifestation	HSCT	ERT	HSCT + ERT
Partial improvement with added benefit of combination therapy			
Cognitive function	Stabilization	No effect	Improvement
Pulmonary function	Limited improvement	Improvement	Improvement
Skeletal manifestations	• Minimal effect of linear growth • Improved facial features and odontoid hypoplasia	No effect	Improved growth rate
Partial improvement			
Upper respiratory	Improvement	Improvement	Improvement
Joint mobility	Improved range of motion	Improved range of motion (shoulder)	NA
Cardiac function	• Improved cardiac hypertrophy and coronary artery narrowing • No effect on valve insufficiencies	• Improved cardiac hypertrophy and ventricular function • No significant effect on cardiac valve thickening	Improvement
Limited effect			
Hearing loss	Improvement/ stabilization	No effect	NA
Corneal clouding	Limited stabilization	No effect	NA
Retinal dysfunction	No effect	No effect	NA
Hearing loss	Improvement/ stabilization	No effect	NA

Open in a separate window

Weekly ERT, approved in 2003, improves some but not all somatic disease manifestations.

Hampe CS et al 2021

18-year sibling study in attenuated MPS I

Siblings started ERT at 5 years old (sister) and 5 months old (brother) and demonstrate substantial difference in impact when ERT is started before significant disease manifestations

- Older sibling had progression of joint disease with carpal tunnel syndrome, shoulder stiffness and TMJ dysfunction. Moderate b/l conductive and sensorineural hearing loss and cardiac valve disease stabilized. Mild obstructive sleep apnea.
- Younger sibling (at 18yo) had no respiratory dysfunction, no large joint arthropathy, no hearing loss, attained adult height 25th%ile
- *Both siblings had progression of corneal clouding*
- Highlights the importance of early identification and early intervention before disease irreversible

Pjetraj D, 2023

IGURE 1 Patient F (24 Y) and Patient M (18 Y) after 18 years of
RT therapy

MPS II, Hunter syndrome

MPS II, also known as Hunter syndrome, is a rare X-linked recessive disorder caused by deficiency of the lysosomal enzyme iduronate-2-sulfatase leading to accumulation of GAGs in nearly all cell types, tissues and organs.

Early, severe neuronopathic presentation with progressive cognitive decline, airway involvement and cardiac disease with death in first or second decade

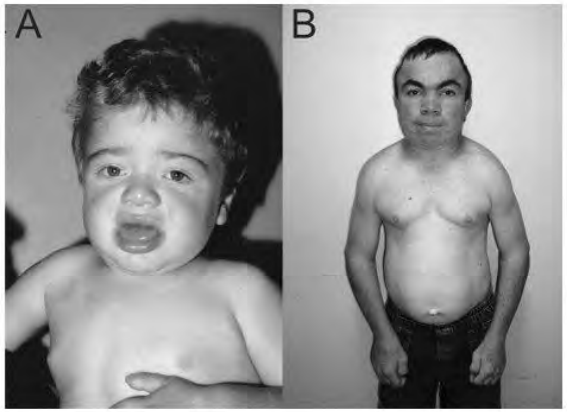


Figure 2 - Children with Hunter syndrome. A: a 2-year-old with a severe phenotype; B: an adult male with an attenuated phenotype.

Attenuated phenotype with joint disease, airway and cardiac valve involvement, rod dystrophy and survival into adulthood with normal cognition

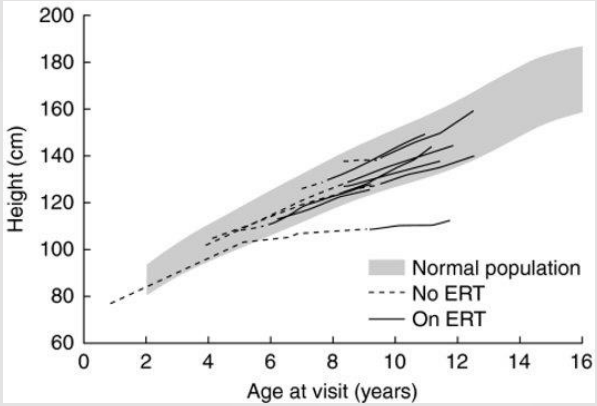
Giugliani, 2014

Enzyme replacement therapy remains standard-of-care for MPS II

Early signs/symptoms of MPS II that trigger clinical suspicion include umbilical hernia, protuberant abdomen, upper respiratory infections and recurrent otitis, joint stiffness with coarse facial features. Average age of onset of symptoms in untreated children has been reported as 1.5 years in severe phenotype and ~4 years for attenuated phenotypes (Kiselyov 2007)

ERT positively influences growth velocity in MPS II

- Short stature linked to dysostosis multiplex (epiphyseal dysplasia and degenerative joint disease)
- Growth in attenuated patients tends to follow normal trajectory until ~ 8 years old after which growth is markedly reduced
- Some limited evidence that earlier ERT initiation improves growth trajectory



**exception, 1 child who was below -2SD at the time of ERT initiation, +nAbs*

Żuber Z 2014

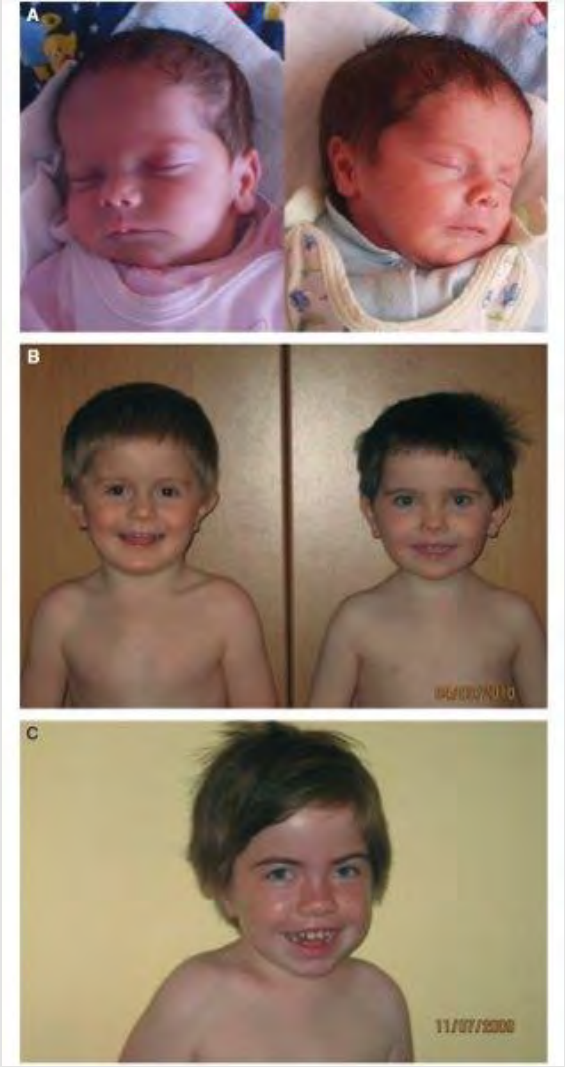
Sibling report of early idursulfase initiation at 3 months

ERT initiated at 3 months

At 3 years old:

- no evidence of coarse facial features, joint disease or organomegaly
- Cardiac function remained normal
- No evidence of dysostosis multiplex
- Demonstrated mild developmental delays compare with twin brother

Tylki-Szymanska A, 2012



Conclusions

- MPS I and II are progressive, multisystemic lysosomal storage disorders with a phenotypic spectrum of clinical disease from early severe neuronopathic disease to attenuated milder somatic disease
- Earliest manifestations of both disorders include umbilical hernia, protuberant abdomen, macrocephaly, distinctive facial features, varying degrees of developmental delays, frequent upper respiratory infections and otitis media with and without hearing loss
- While HSCT is standard of care for severe MPS I given its demonstrated ability to stabilize neurocognitive decline if performed early (< 24-36 months old), enzyme replacement therapy remains standard of care for MPS II and attenuated forms of MPS I
- Evidence suggests earlier initiation of ERT results in improved clinical outcomes despite known limitations of ERT necessitating further therapeutic development to target compartments such as eye, CNS and joints
- Evidence of improved outcomes with earlier intervention supported RUSP nomination and approval for MPS I in 2016 and MPS II in 2022

Other LDs Not Yet Included in RUSP: Expanding Early Therapy for Fabry Disease

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Uma has received honoraria for this talk. Uma has received honoraria for lectures and/or advisory boards from Amicus, Chiesi, Sanofi and Takeda; and Institutional research grants from Amicus, Chiesi, Intrabio and Takeda.

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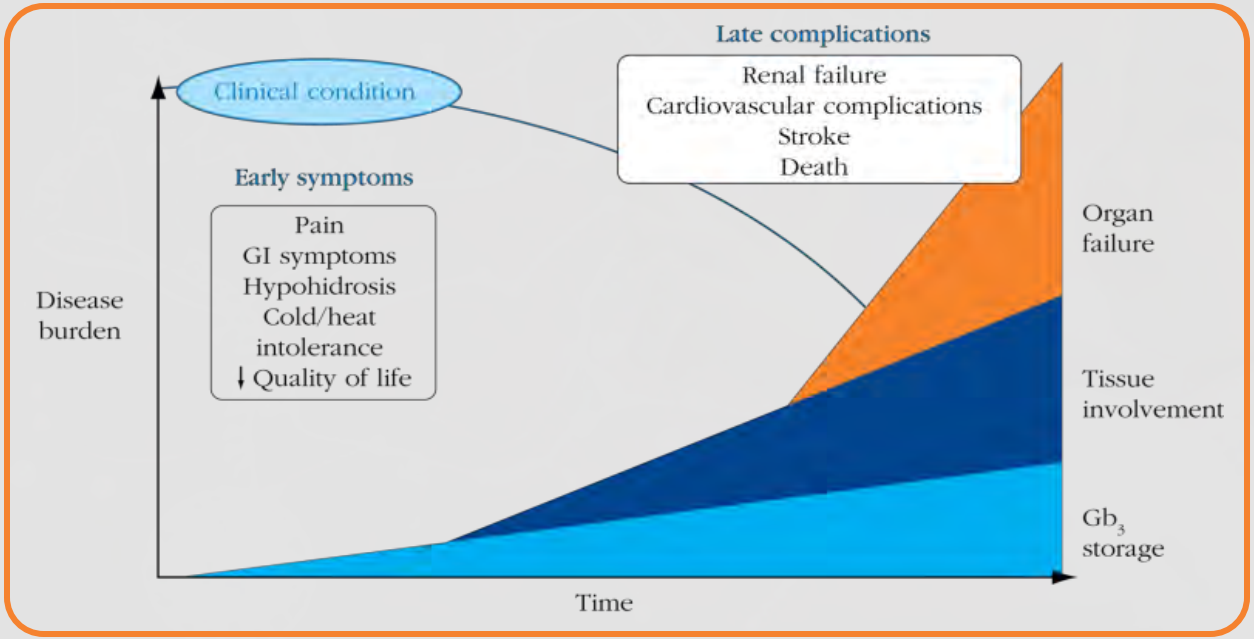
Grand Hall AB

Progressive Pathology: Fabry Disease Model



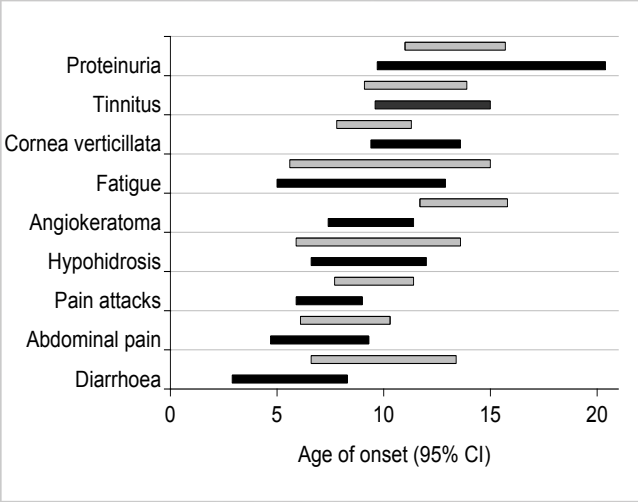
Gb_3: globotriaosylceramide; ERT enzyme replacement therapy.

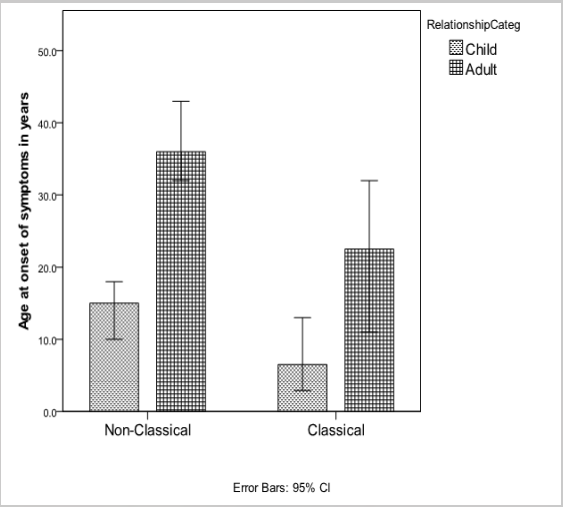
Fabry Disease Therapies

- 1st generation ERT adults and children (agalsidase alfa and agalsidase beta)
- Pegylated ERT (pegunigalsidase for adults and in clinical trials for children)
- Oral chaperone (migalastat) licensed over 12 years of age for amenable *GLA* variants
- Other novel therapies including gene therapy and substrate reduction therapies are currently under clinical trials in adults

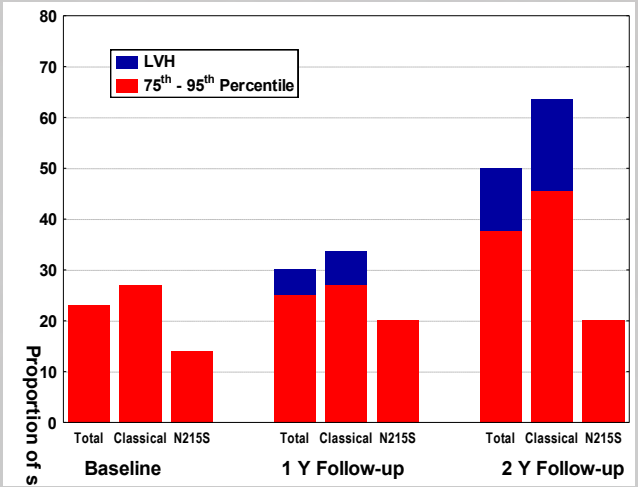
Adapted from Eng et al. *J Inherit Metab Dis* 2007
Han-Wook Yoo et al 2023

Age at Onset & Common Clinical Manifestations in Children

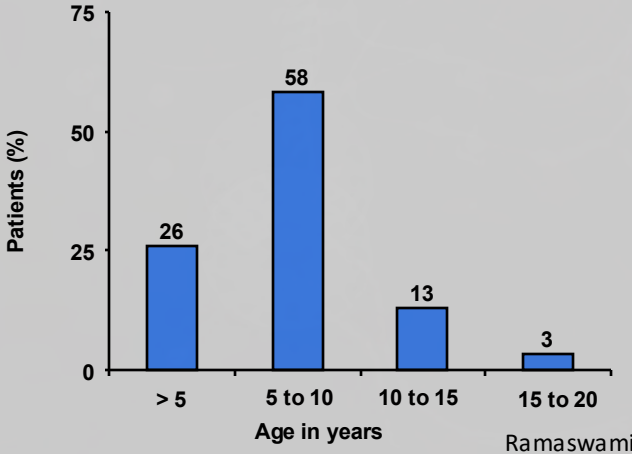




Ramaswami 2011 – personal data, unpublished

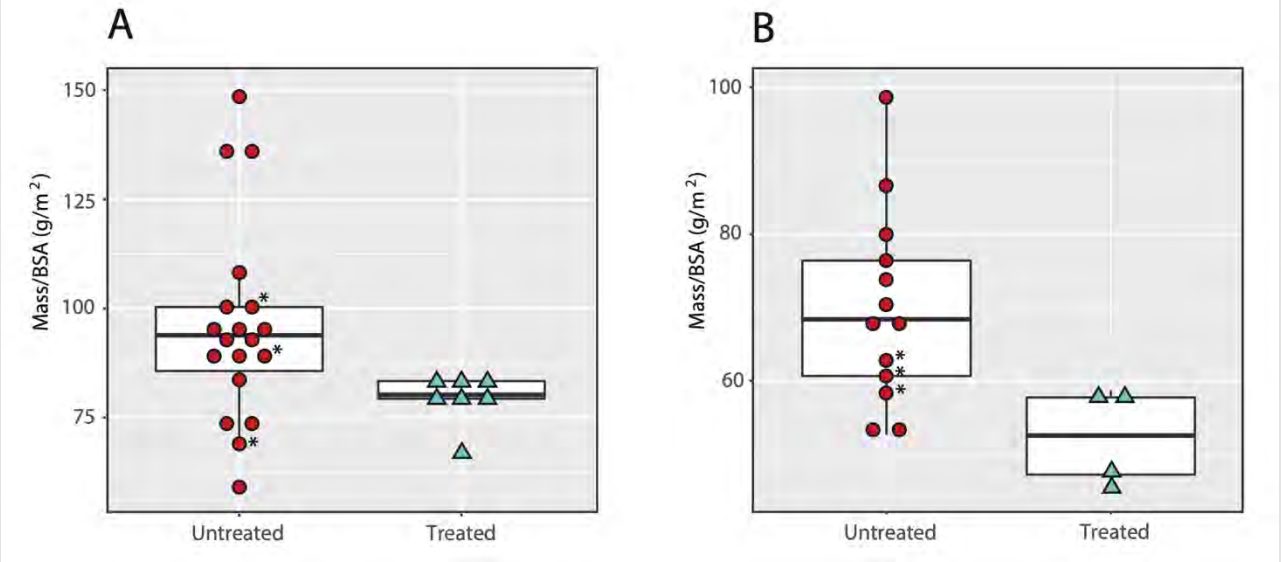


Havranek et al 2013



Ramaswami et al 2003

Early start of enzyme replacement therapy in pediatric male patients with classical Fabry disease is associated with attenuated disease progression



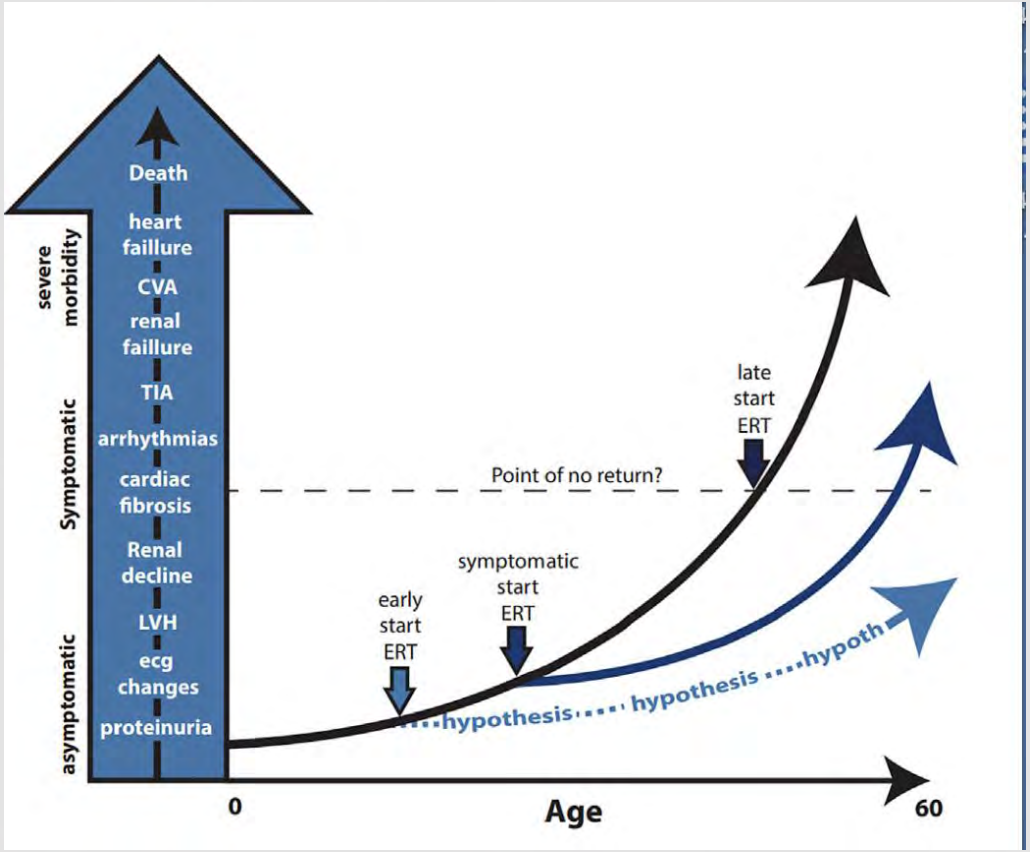
n = 7, males; classical phenotype. ERT commenced before 16 years of age.

Analyses 10 years after commencing ERT.

Compared with untreated males: n = 23, median age 22 years, range 13–27).

S.J. van der Veen et al. MGM 2022

Hypothesis on attenuation of disease progression with early start of disease modifying therapy



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Fabry Disease Newborn Screening (NBS): Enzymatic and Molecular Assays

First Tier Tests

Enzymatic Assays:

- Digital Microfluidics
- Tandem Mass Spectrometry
- Fluorometry
- Immune quantification

Molecular Assays:

- High resolution melting (covers the 7 GLA exons but Low sensitivity for variants in exons 2 and 6)
- Agena iPlex (known pathogenic variants)

Second Tier tests:

- Genetic testing is complicated by variants of unknown significance and unclassified variant
- Plasma lysogb3 is informative in classical males;
  mild to moderately elevated in
  late onset phenotypes and females
- Plasma lysogb3 not always elevated in infants diagnosed by NBS

Gragnaniello V et al. 2023

The most important FD pilot studies and screening programs worldwide.

Study Period	Country	Method	Type of Cutoff	Number of NBS Samples	Number of below Cutoff Samples	Number of below Cutoff Samples/ 100,000 Newborns	Confirmed Patients from Genetic Analysis *	Presumed Incidence **	Source of Data
USA									
2011–2013 ***	California	MS/MS, immuno-capture assay, DMF (compara-tive)		89,508 (m 44,664) (deidentified)	Variable based on method	Not applicable	50 (m 46)	1:1790 (m 1:1970)	Sanders et al. [34]
2013 **	Washington State	MS/MS	%DMA	108,905 (m 54,800) (deidentified)	16 (m 13)	15 (m 24)	7 (m 7)	1:15,558 (m 1:7800)	Scott et al. [62]
2013	Missouri	DMF	fixed	43,701	28	64	15 (m 15)	1:2913	Hopkins et al. [14]
2013–2019	New York	MS/MS	% DMA	65,605	31	47	7 (m 7)	1:9372	Wasserstein et al. [63]
2014–2016	Illinois	MS/MS	% DMA	219,793	107	49	32 (m 32)	1:6968	Burton et al. [64]
2016 ***	Washington State	MS/MS	% DMA	43,000 (deidentified)	8	19	6	1:7167	Elliot et al. [38]
Latin America									
2012–2016	Petroleos Mexicanos Health Services	MS/MS	fixed	20,018 (m 10,241)	5 (m 5)	25 (m 49)	5 (m 5)	1:4003 (m 1:2048)	Navarrete-Martinez et al. [65]
2017	Brazil	DMF	fixed	10,527	0	0	0	/	Camargo Neto et al. [66]

Summary of NBS Incidence in Fabry Disease: predominance of late onset variants

- **Europe:** 1 in 3100 (Italy) to 1 in 13, 341 (Hungary)
- **Asia:** 1 in 1222 (Japan) to 1 in 12,982 (China); Taiwan 1 in 2393 (86% late onset cardiac variant)
- **USA**: 1 in 1790 (California) to 1 in 15,558 (Washington State)

Gragnaniello V et al. 2023

Newborn Screening in Fabry Disease

Advantages	Disadvantages
Available methods for NBS on DBS	Enzyme based assays do not identify many female heterozygotes.
Approved treatments	Higher than expected numbers of later onset forms
Importance of early diagnosis and treatment, often delayed clinical diagnosis	Lack of definite guidelines for follow up and start therapy especially for later onset forms
Better knowledge of the natural history	Frequent detection of VUS or benign variants
Genetic counseling	Phenotype prediction can be difficult
Family screening	
High incidence, more frequent than previously expected	

Abbreviations: DBS: dried blood spot, NBS: newborn screening, VUS: variant of uncertain significance.

Diagnostic confirmation and management of presymptomatic Fabry Disease

Timing	Suggested Tests
Diagnostic confirmation	Genetic analysis * (patient and parents), substrate quantification (plasma lysoGb3) and enzyme activity in leukocytes, lymphocytes or plasma (in males).
Baseline diagnostic studies	ECG, echocardiogram, ophthalmologic examination, renal function tests, plasma and/or urine GL3
Follow up every 6 months (classic form) or 12 months (later onset form)	Clinical examination (angiokeratomas, hypohidrosis, gastrointestinal symptoms, limb pain), kidney (eGFR according to Schwartz formula, microalbuminuria, proteinuria), cardiac assessments (ECG, echocardiography, 24-h holter), neurologic evaluation, plasma lyso-Gb3.

* Variants are classified according to published clinical reports and public databases.

Gragnaniello V et al. Int. J. Neonatal Screen. 2023, 9, 31; Wang RY et al 2011.

Conclusions

- **Classic Fabry disease is a progressive life limiting disease.** Newborn screening incidence of classic Fabry disease is about 1 in 37,000.
- **Late-onset Fabry disease** is often misdiagnosed for years. Newborn screening incidence of late-onset Fabry disease is about 1 in 3,100 to 1 in 4,600.
- In the UK Biobank, the prevalence of likely pathogenic Fabry disease-causing variants is 1/5732 for late-onset disease-causing variants and 1/200 643 for variants causing classic Fabry disease
- Classical Fabry Disease: disease progression occurs in all males and some females. Early treatments starting in childhood and before the onset of end organ disease, significantly delays disease progression
- Whilst approximately 60% of *GLA* variants identified by newborn screening are late onset variants, this should not be a reason to exclude Fabry Disease in national newborn screening programmes.
- Newborn screening provides the opportunity to treat classical phenotype patients early; and reverse cascade screening of the parent and extended family members, ending their own long diagnostic odysseys and also enabling them to timely access to disease modifying therapies.
- Urgent unmet need: standardised protocol for management of infants who present with late onset phenotypes in particular, including psychological and social support throughout childhood, whilst not over medicalising.

Gilchrist M, *et al*. 2023; Spada et al. 2006; and
Speaker's opinion from personal experience of management of Fabry Disease

Acid Sphingomyelinase Deficiency Spectrum with multiple subtypes

deficiency of acid sphingomyelinase; SNPD1 gene mutations

TYPE A	TYPE A/B	TYPE B
Acute Neurovisceral	Chronic Neurovisceral	Chronic Visceral
Rapidly progressive with acute multiorgan and neurologic symptoms	Intermediate and multiorgan with varying degrees of neurologic involvement	Chronic and multiorgan with no neurologic involvement
ONSET: *Early infancy*	ONSET: *Infancy to adulthood*	ONSET: *Infancy to adulthood*
LIFE EXPECTANCY: *2–3 years of age*	LIFE EXPECTANCY: *Variable between childhood and early adulthood*	LIFE EXPECTANCY: *childhood and late adulthood*
LEADING CAUSE OF DEATH: *Respiratory failure, multi-system failure*	LEADING CAUSE OF DEATH: *Respiratory disease, liver disease, liver transplant complications, neurodegenerative disease*	LEADING CAUSE OF DEATH: *Respiratory disease, liver disease, bleeding*

ASMD newborn screening:

Europe: 2013 to 2023:PPV 100%
Incidence: 1 in 137,506 (Italy)

USA: 2014 to 2023:PPV 100%
Incidence: 1 in 126,345 (Illinois)

PPV: Positive predictive value

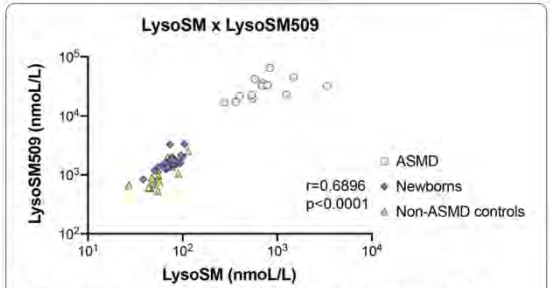

Fig. 3 Pearson's correlation of the lysoSM x lysoSM509 in ASMD patients, controls, and general newborns

Olipudase Alfa for Paediatric ASMD

- First and only approved therapy for chronic visceral ASMD (NPB)
- Improves survival and reduces disease burden in children with visceral ASMD.
- Early diagnosis treatment may modify disease progression

Genotype-Phenotype Correlation:

NPB: missense mutations with residual enzyme activity.

NPA: frameshift and nonsense mutations with complete loss of enzyme function.

Population-specific mutations: founder effects (Ashkenazi Jewish population).

Wasserstein M et al 2015; McGovern M et al. 2006; Schuchman E et al 2007; McGovern M et al. 2008; McGovern M *et al*. 2013; Gragnaniello V et al. 2024; Kubaski et al 2022; Wasserstein M and E Schuchman 2023; Wang R et al 2023; Geberhiwot T et al 2023; Diaz GA et al 2021 and 2022; Yu-wen Pan et al 2023.

Thank you

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