Treatments for LSDs

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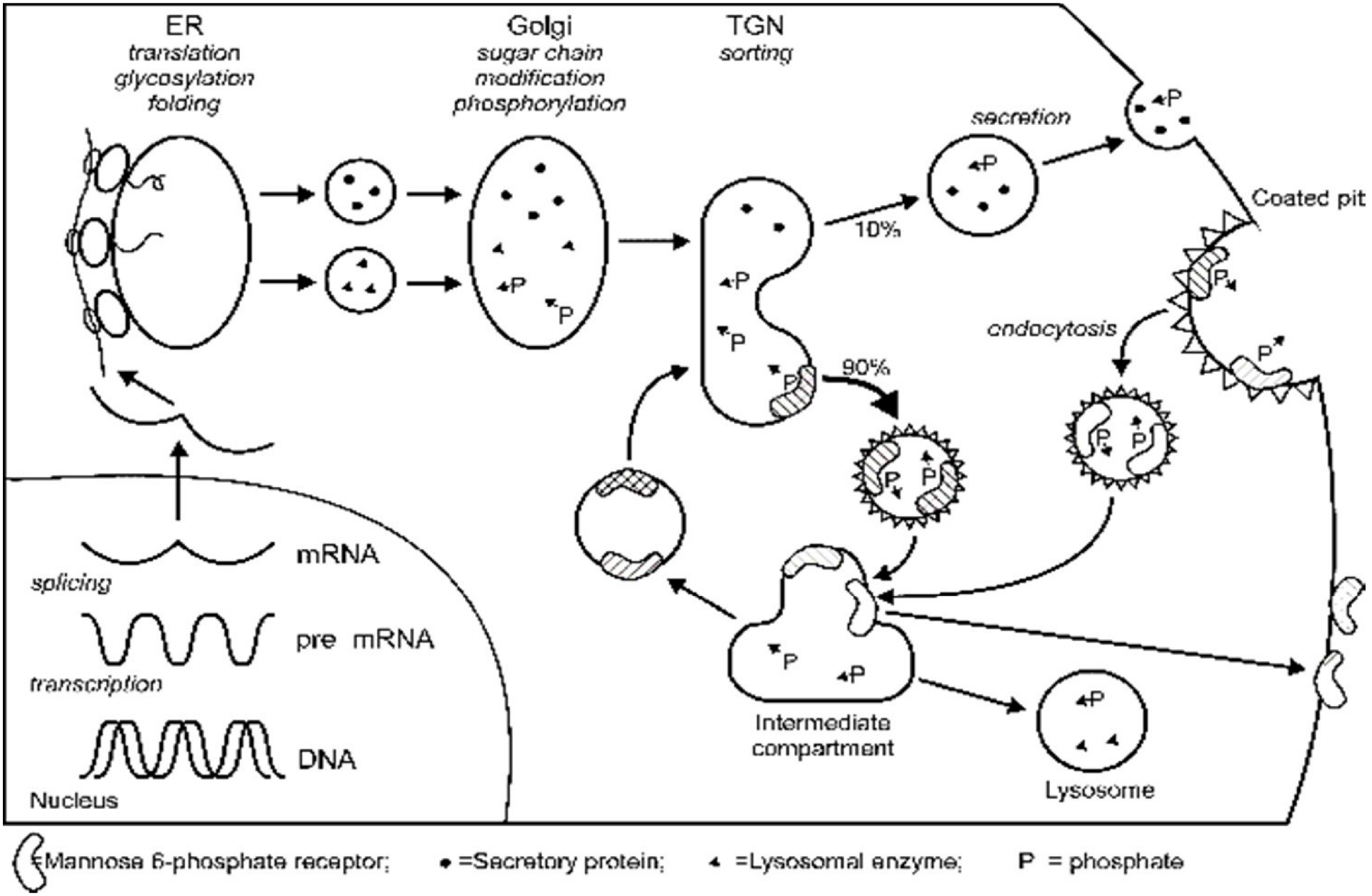
Management of LSDs

- Multidisciplinary supportive care
  - No treatments currently available negate the need for a team of experienced specialists

- Treatments aimed at underlying defects
  - Enzyme replacement therapy (ERT)
  - Haematopoietic stem cell therapy (HSCT)
  - Substrate reduction therapy

Cross correction of enzyme



Courtesy of Ans Van der Ploeg

Disease modifying treatments

ERT

Gaucher disease (x2)

Fabry (x2)

MPS I - 2003

MPS II - 2007

MPSIVA - 2014

MPS VI - 2007

Pompe

LAL deficiency

LINCL (CLN2)

MPSVII

HSCT

MPSI - Hurler phenotype

Mannosidosis

MPSII – for CNS disease if very early

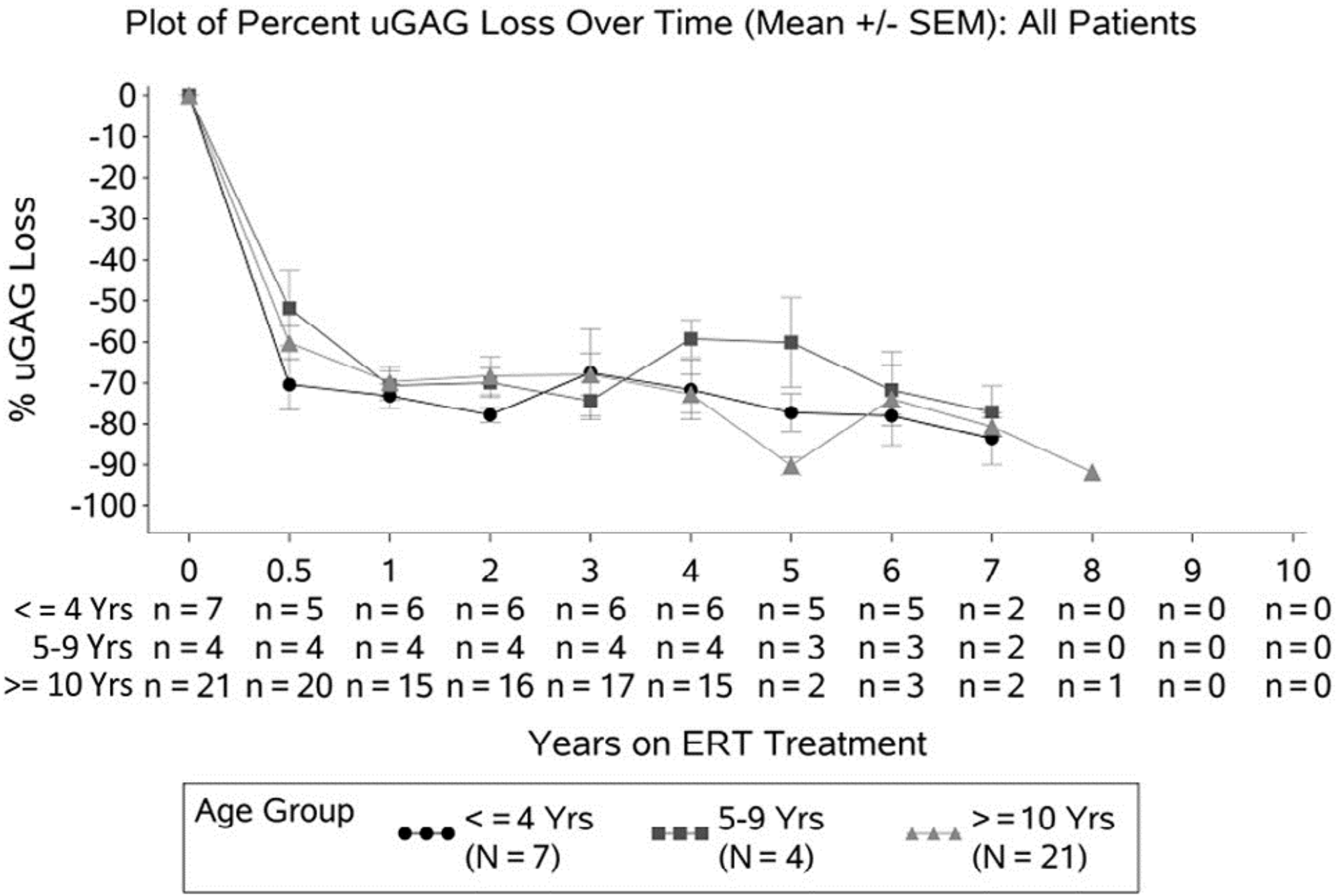
Small molecules:

Fabry

Gaucher

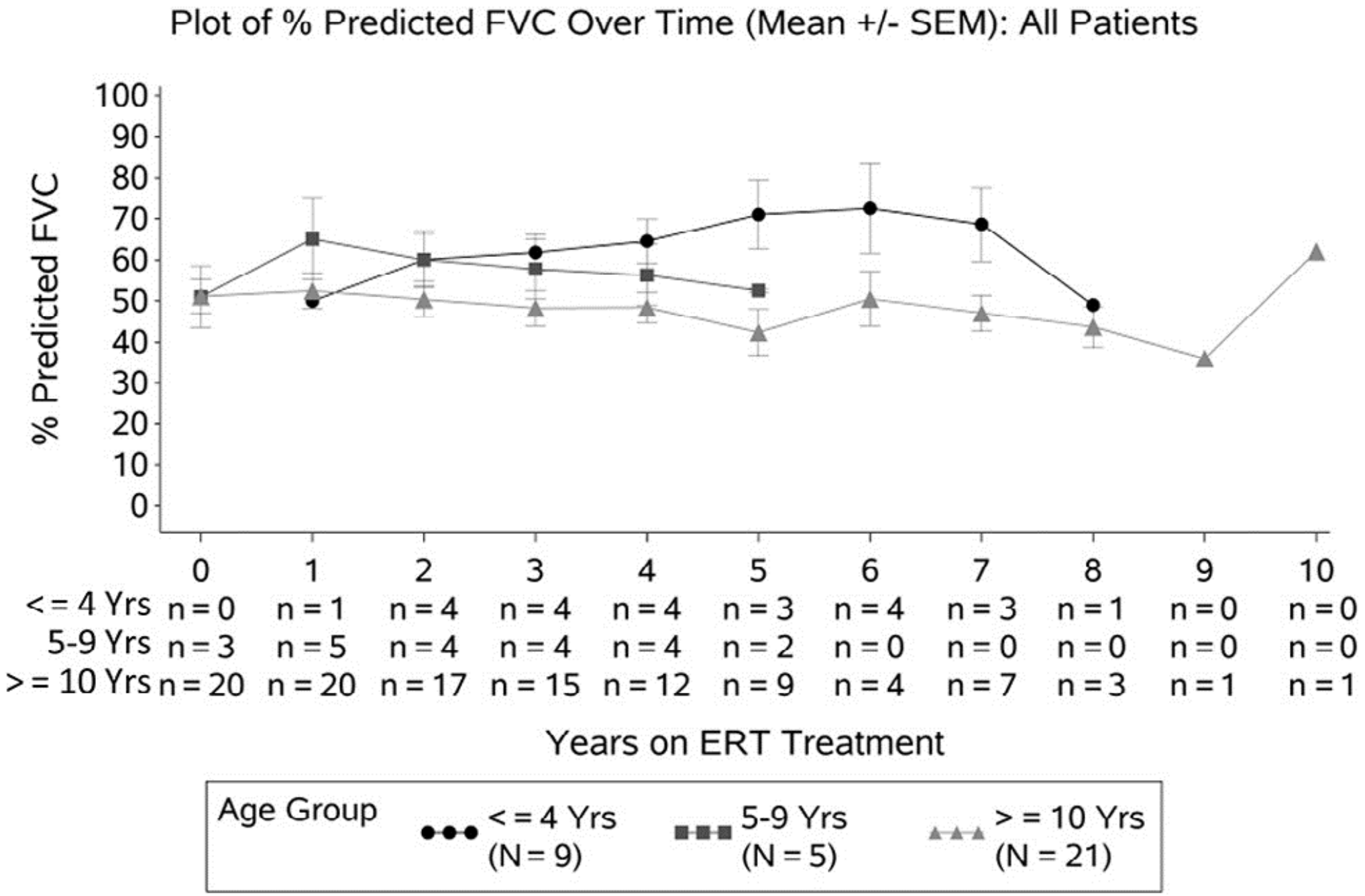
NPC

A

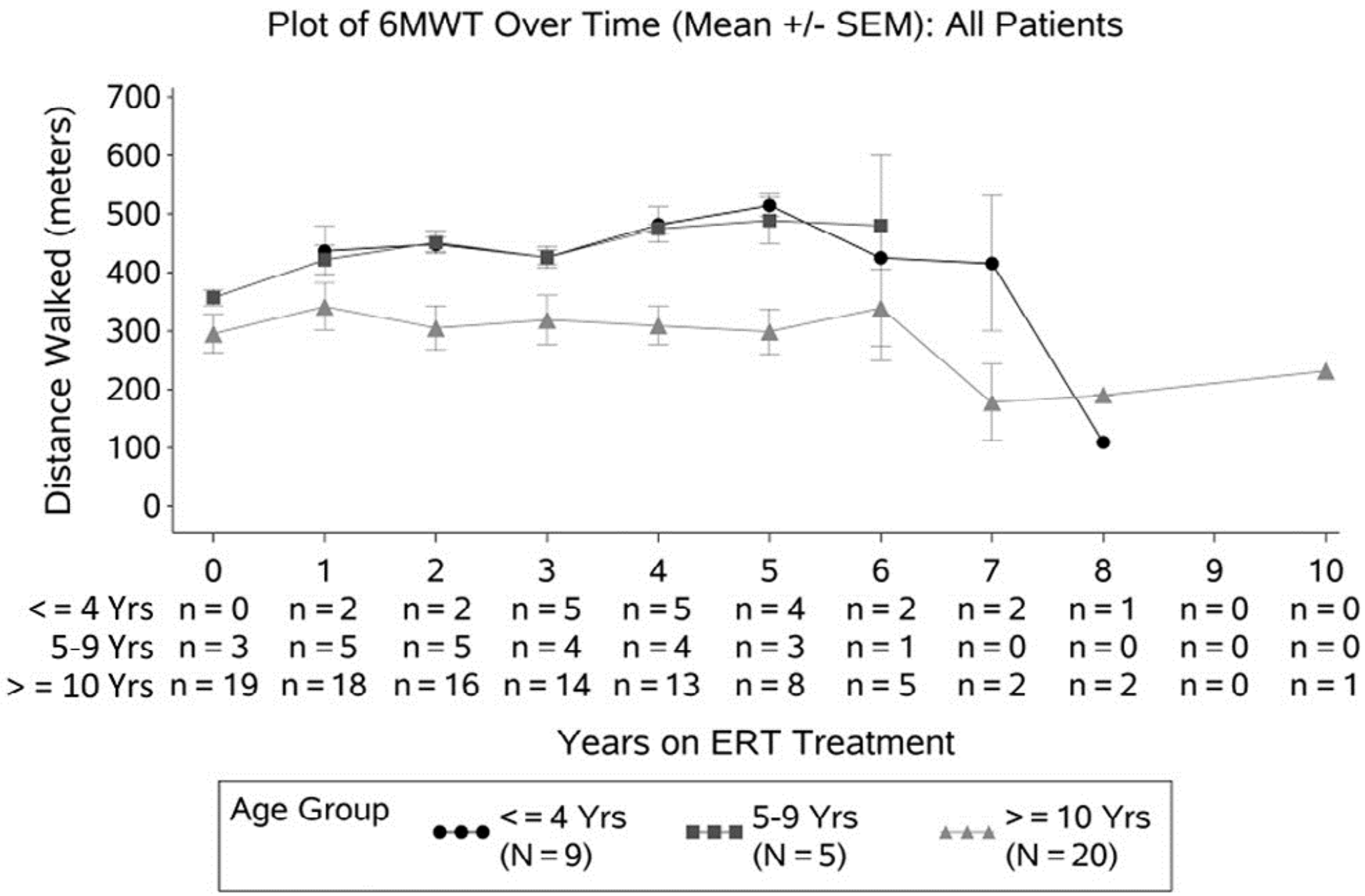


Laraway et al Jpeds 2016

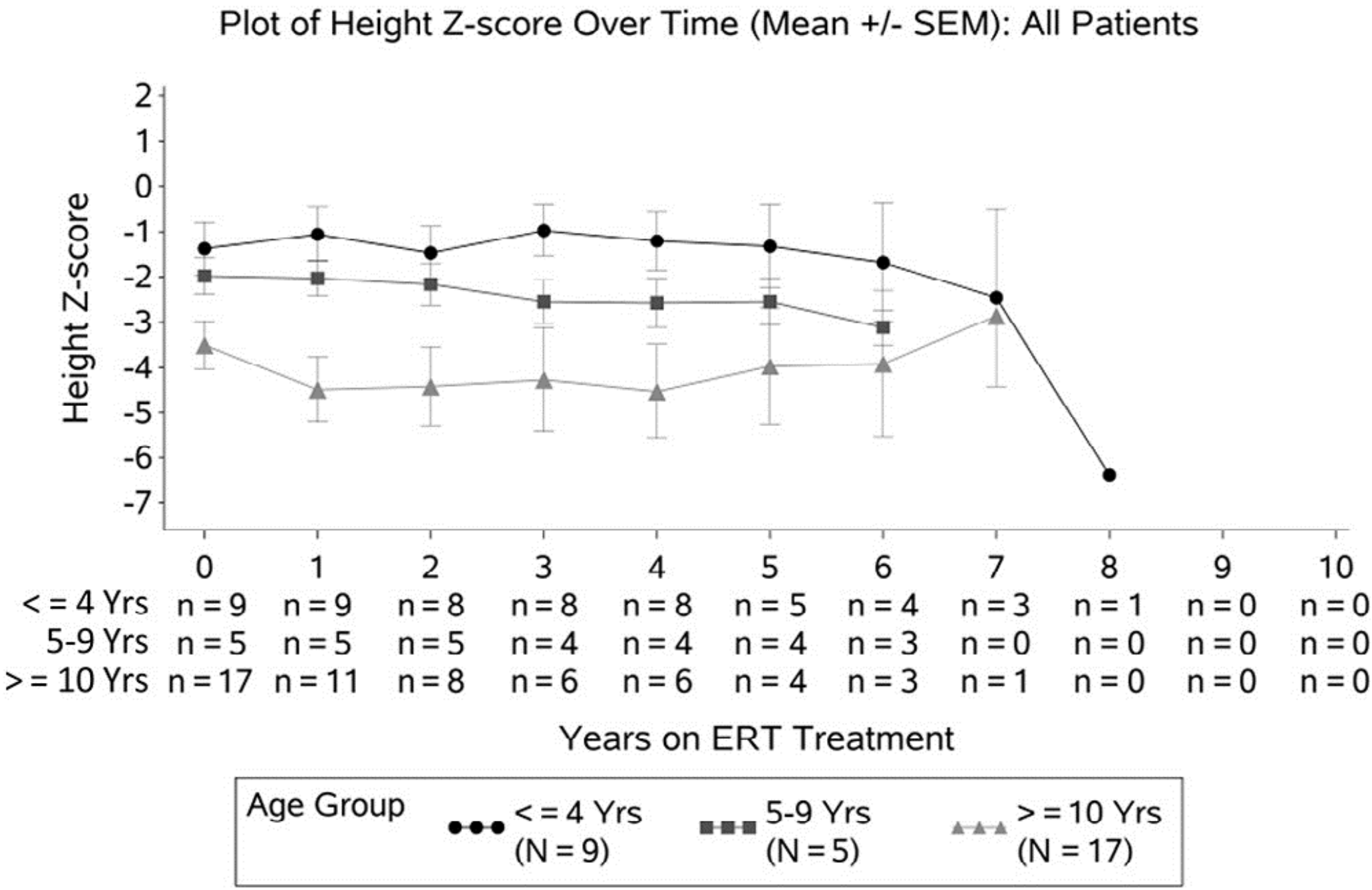
C


Plot of % Predicted FVC Over Time (Mean +/- SEM): All Patients
% Predicted FVC
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10
< = 4 Yrs n = 0 n = 1 n = 4 n = 4 n = 4 n = 3 n = 4 n = 3 n = 1 n = 0 n = 0
5-9 Yrs n = 3 n = 5 n = 4 n = 4 n = 4 n = 2 n = 0 n = 0 n = 0 n = 0 n = 0
> = 10 Yrs n = 20 n = 20 n = 17 n = 15 n = 12 n = 9 n = 4 n = 7 n = 3 n = 1 n = 1
Years on ERT Treatment
Age Group
< = 4 Yrs (N = 9)
5-9 Yrs (N = 5)
> = 10 Yrs (N = 21)

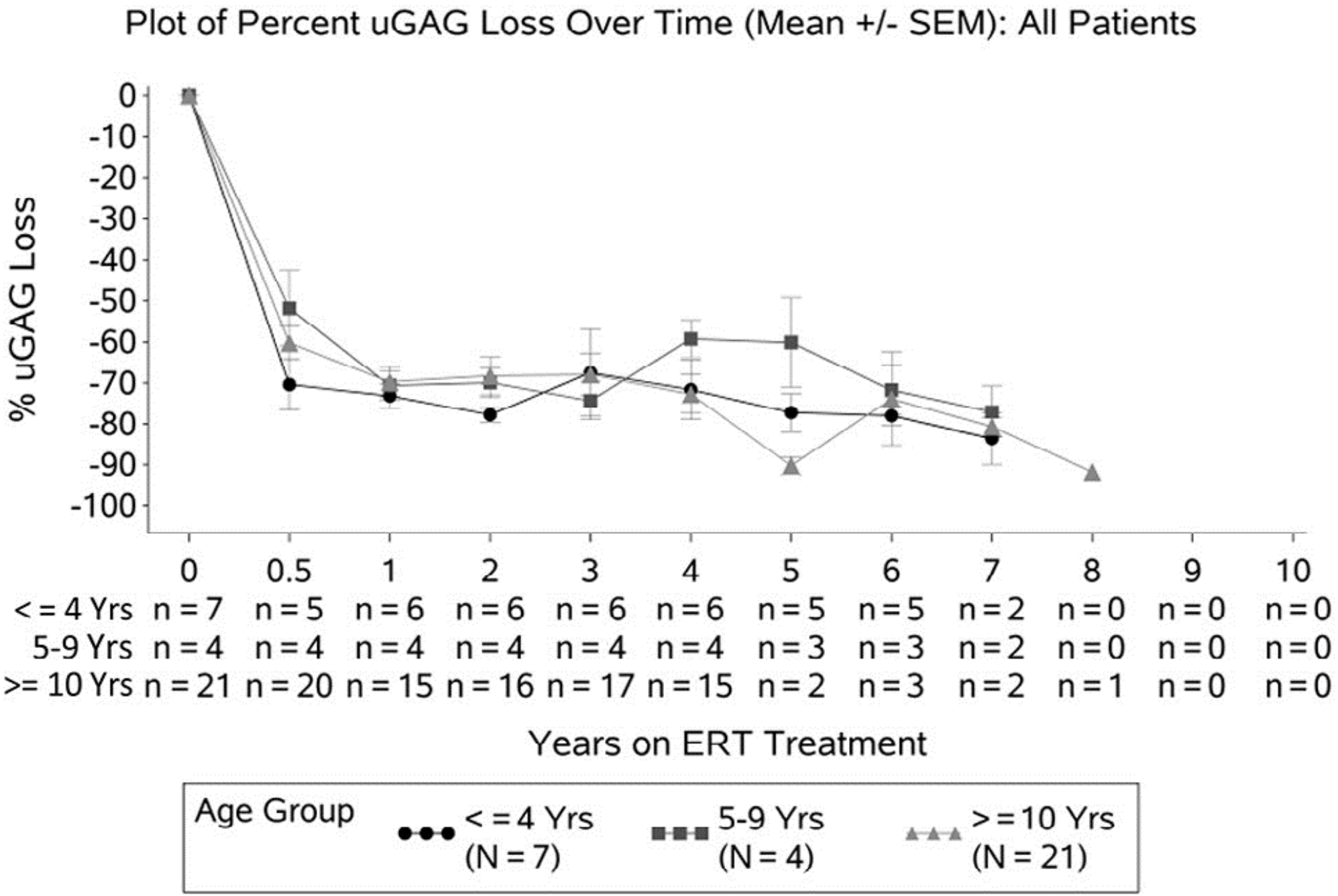
D


Plot of 6MWT Over Time (Mean +/- SEM): All Patients
Distance Walked (meters)
700
600
500
400
300
200
100
0
0 1 2 3 4 5 6 7 8 9 10
< = 4 Yrs n = 0 n = 2 n = 2 n = 5 n = 5 n = 4 n = 2 n = 2 n = 1 n = 0 n = 0
5-9 Yrs n = 3 n = 5 n = 5 n = 4 n = 4 n = 3 n = 1 n = 0 n = 0 n = 0 n = 0
> = 10 Yrs n = 19 n = 18 n = 16 n = 14 n = 13 n = 8 n = 5 n = 2 n = 2 n = 0 n = 1
Years on ERT Treatment
Age Group
< = 4 Yrs (N = 9)
5-9 Yrs (N = 5)
> = 10 Yrs (N = 20)

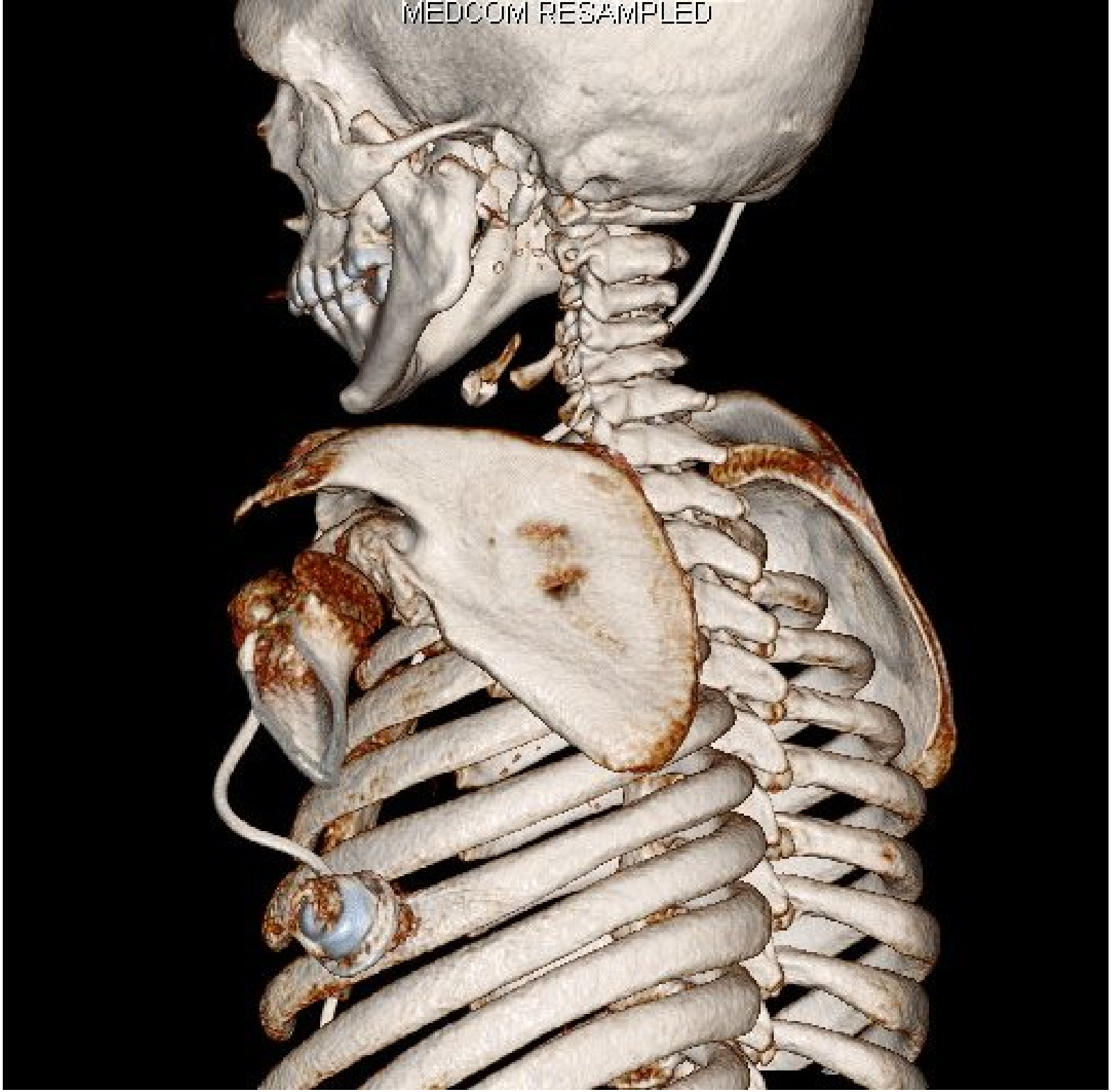
B

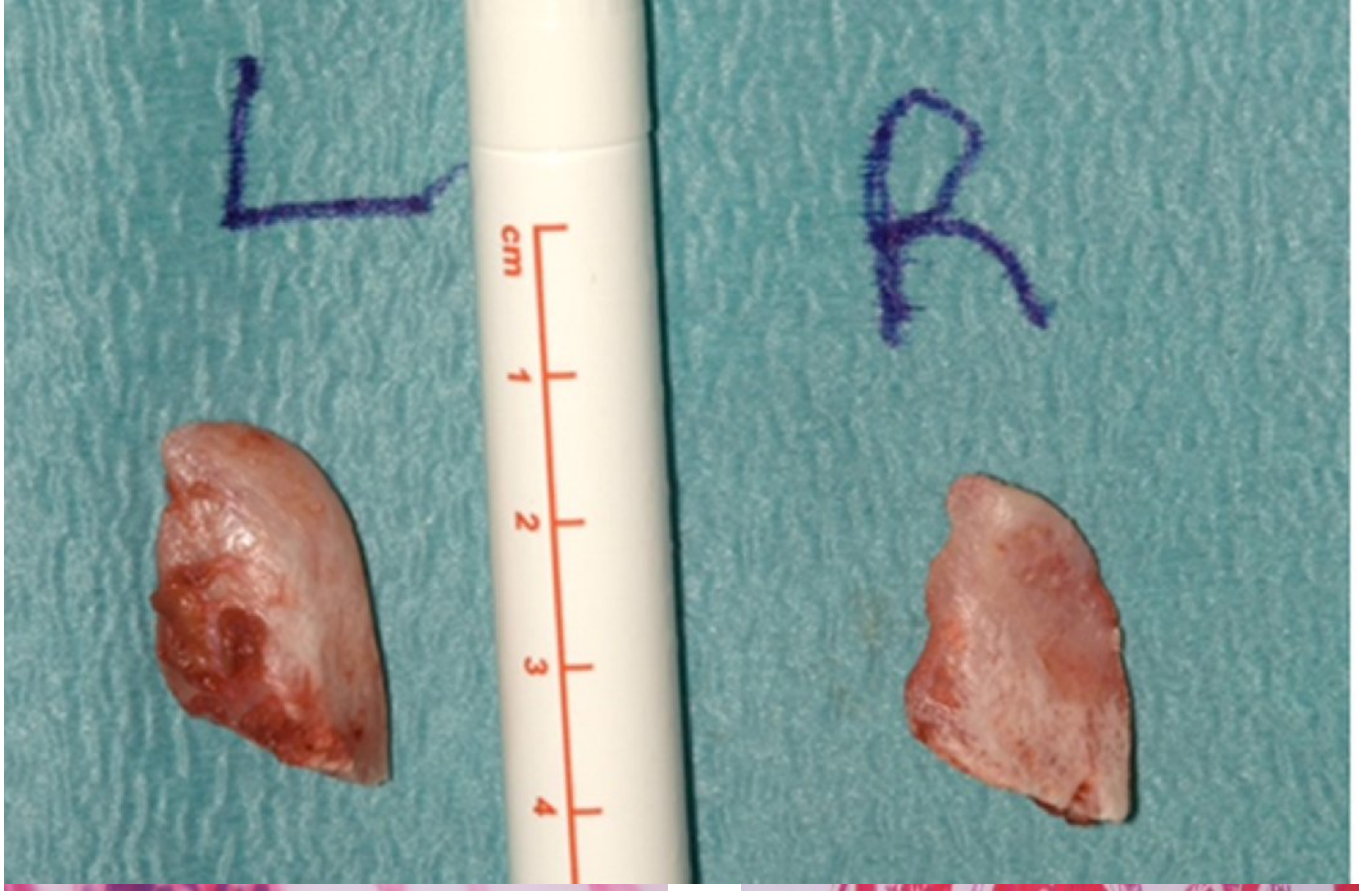

Plot of Height Z-score Over Time (Mean +/- SEM): All Patients
Height Z-score
2
1
0
-1
-2
-3
-4
-5
-6
-7
0 1 2 3 4 5 6 7 8 9 10
< = 4 Yrs n = 9 n = 9 n = 8 n = 8 n = 8 n = 5 n = 4 n = 3 n = 1 n = 0 n = 0
5-9 Yrs n = 5 n = 5 n = 5 n = 4 n = 4 n = 4 n = 3 n = 0 n = 0 n = 0 n = 0
> = 10 Yrs n = 17 n = 11 n = 8 n = 6 n = 6 n = 4 n = 3 n = 1 n = 0 n = 0 n = 0
Years on ERT Treatment
Age Group
< = 4 Yrs (N = 9)
5-9 Yrs (N = 5)
> = 10 Yrs (N = 17)

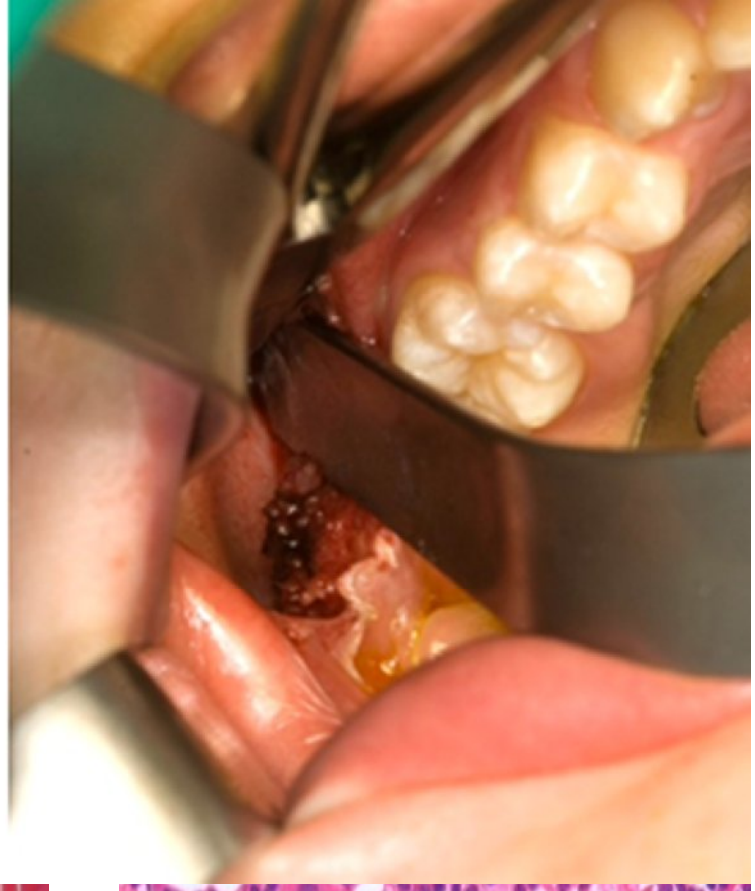
A

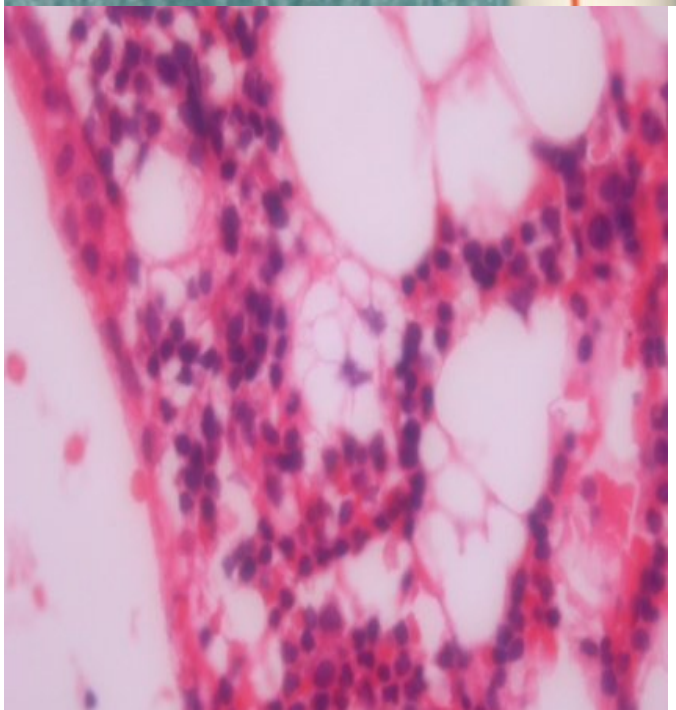


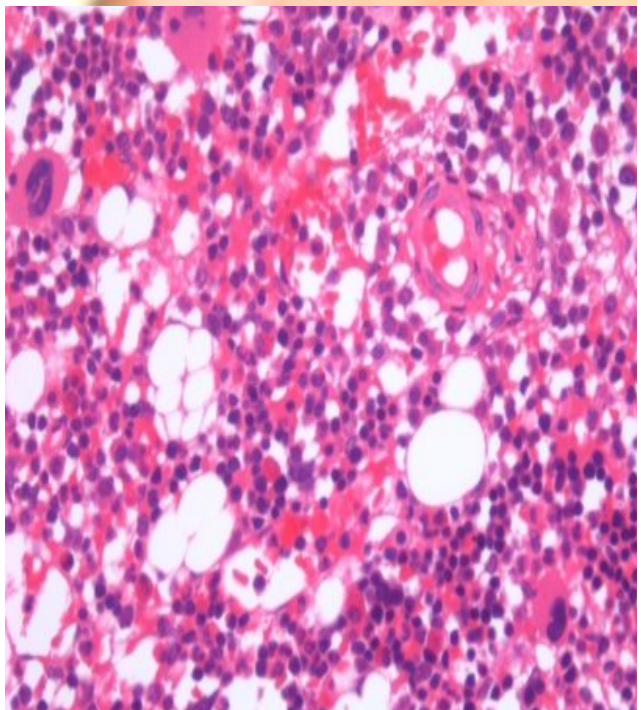
Laraway et al Jpeds 2016


MEDCOM RESAMPLED


L
R
cm
1
2
3
4





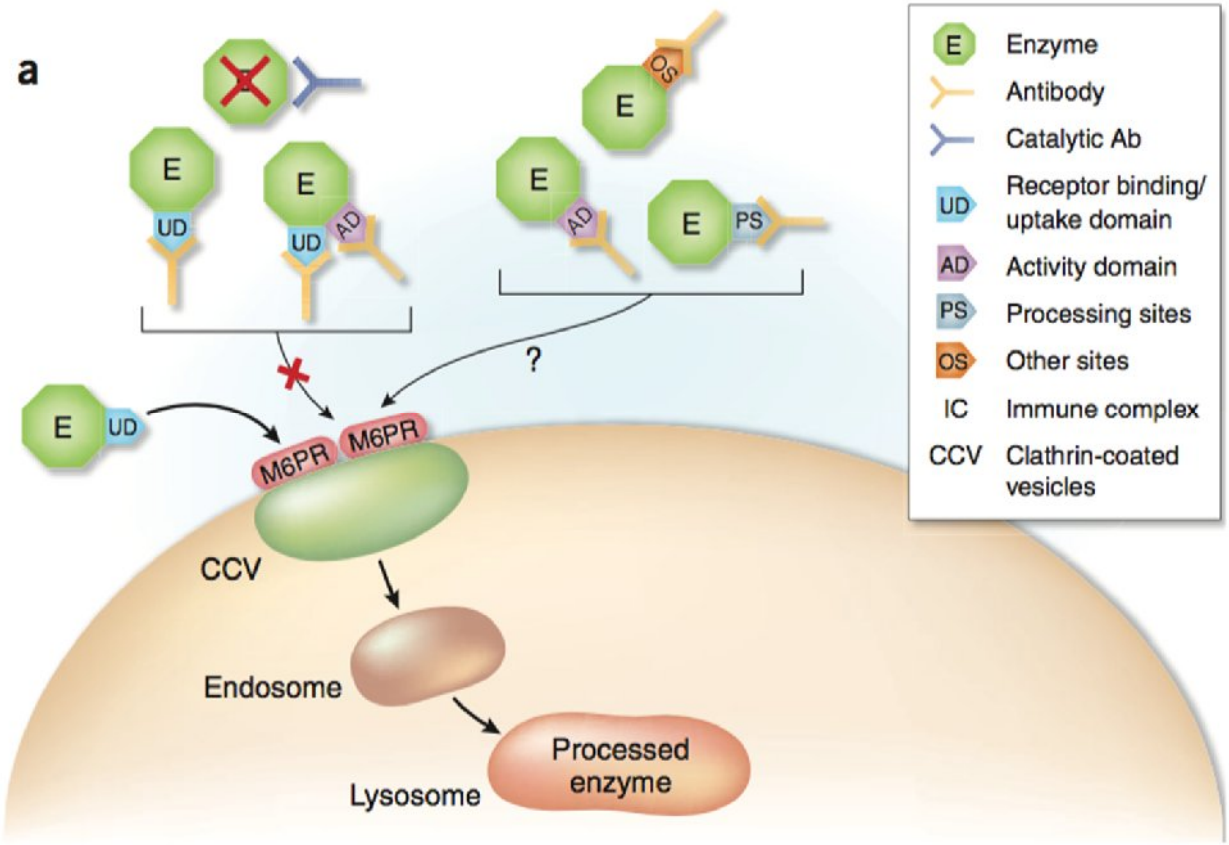


Does a normal urine GAG mean substrate is reduced to normal?

Example from MPSVI

- 14 year old boy presents with back pain from age 3
- 182 cm tall
- x rays show mild degenerative changes, not diagnostic
- Total uGAG within normal range, 2D showed spot of dermatan sulphate
- Y210C homozygous

Potential mechanisms for antibody mediated effects on therapeutic proteins



Wang (2008), Nat Biotechnol

CRIM-negative status predicts poorer clinical outcome

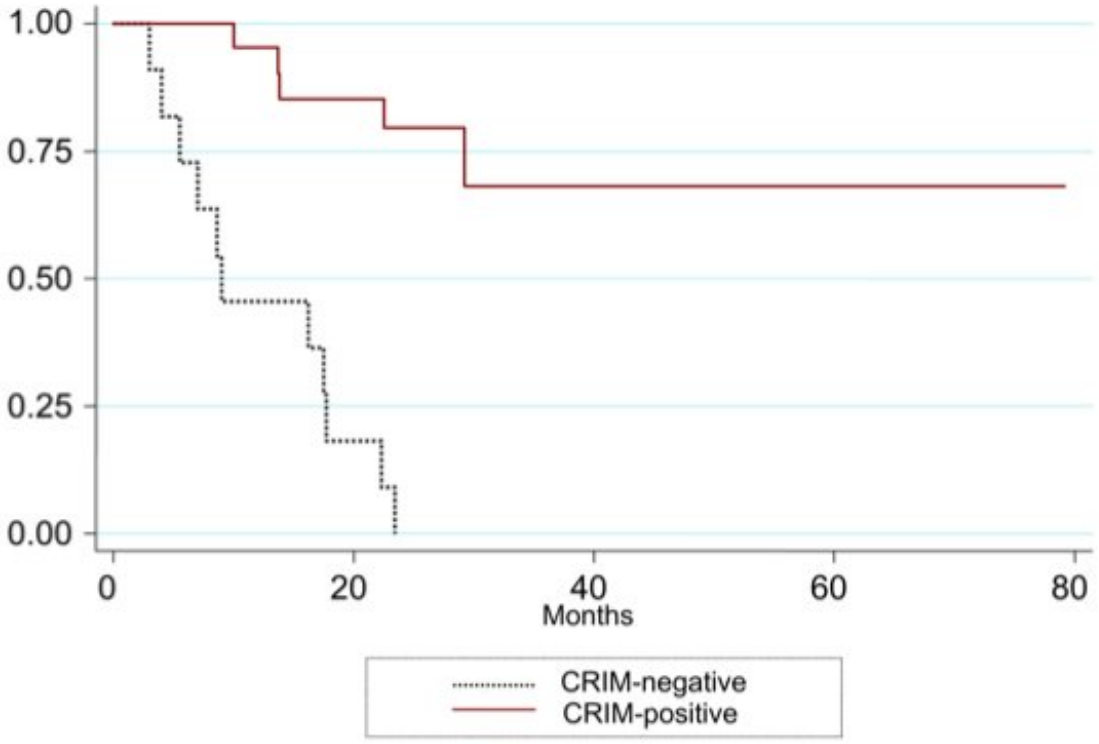


Fig. 2.
Kaplan–Meier curve of ventilator-free survival of the CRIM-negative ($n = 11$) and CRIM-positive ($n = 21$) patients.

Kishnani (2010)

IgG antibody response to ERT is common across lysosomal storage disorders

SSIEM 2015

The impact of the immune system on the safety and efficiency of enzyme replacement therapy in lysosomal storage disorders

A. Broomfield[1] · S. A. Jones[1] · S. M. Hughes[2] · B. W. Bigger[3]

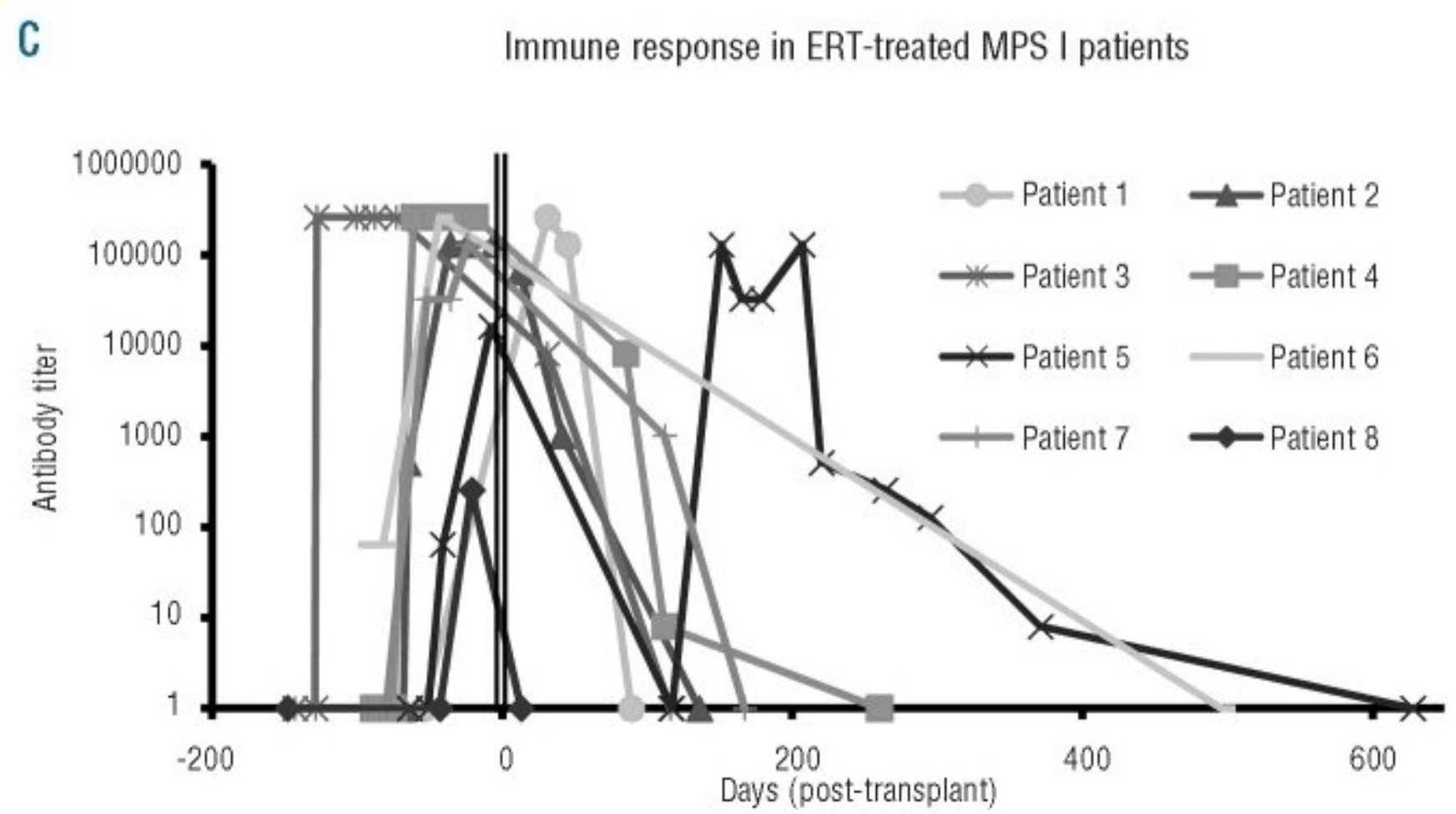
Table 3 Overview of antibody response to ERT

Disease	Number of patients in study (age)	Drug	IRR	IgE	IgG	Nabs	Paper
MPS 1	45 (>5y)	α-l-iduronidase		0/3	20/22 = 91 %	–	Wraith et al (2004)
MPS 1	45 (>5y)	α-l-iduronidase	26 % NRTT	1	42/45 = 93 % → 29 % tolerazing	–	Clarke et al (2009)
MPS1	20 (<5y)	α-l-iduronidase	35 % NRTT	0/2	20/20 = 100 %	–	Wraith et al 2007
MPS II	6 (<6y)	Idursulfase beta	17 %	–	66 %	66 %	Sohn et al (2015)
MPS II	124 (<6y) 287 (>6y)	Idursulfase	27 % 17 %	0	38/71 = 54 % 71/166 = 43 %	–	Muenzer et al (2011b)
MPs IV	176 (>5y)	Elosulfase	NRTT	10 %	100 %	98 %	Schweighardt et al 2015 (2015)
MPS VI	39	Galsulfase	58 %	–	38/39 = 97 %	–	Harmatz et al 2006 (2006)
MPS VI	48	Galsulfase	–	–	43/48 = 91 %	77 %	White et al (2008)
Gaucher	211 overall 6 naïve (8< 17 years)	Velaglucerase	13.3 % NRTT	0	17.5 % ***	5.2 % ***	Pastores et al (et al 2014)
Gaucher	1122	Imiglucerase	–	–	142/1,122 = 13 %	–	Rosenberg et al (1999)
Gaucher	262 adult	Alglucerase	14/262 = 5 %		32/262 = 12 %	–	Richards et al (1993)
Fabry	Men = 571 Women = 251	Agalsidase beta	26 % 17 %	–	M 416/571 = 73 % F 31/251 = 12 %	–	Wilcox et al (2012)
Fabry	Men = 41 Women = 38	Agalsidase beta and alfa	ab+ve = 89 % ab –ve = 26 %	–	M=46 % F=0		Smid et al (2013)
Pompe		Alglucosidase alfa	20/39 51 %				El-Gharbaway et al (2011)
Pompe	18 (<1 y)	Alglucosidase alfa	11/18 = 61 %		16/18 = 88 %	3 pt > 20 % activity	Kishnani et al (2009)

*** Positive for anti-imiglucerase at baseline

NRTT—no relationship with titer. NABs—neutralizing antibody titer

Almost all patients develop high titre antibodies to ER-

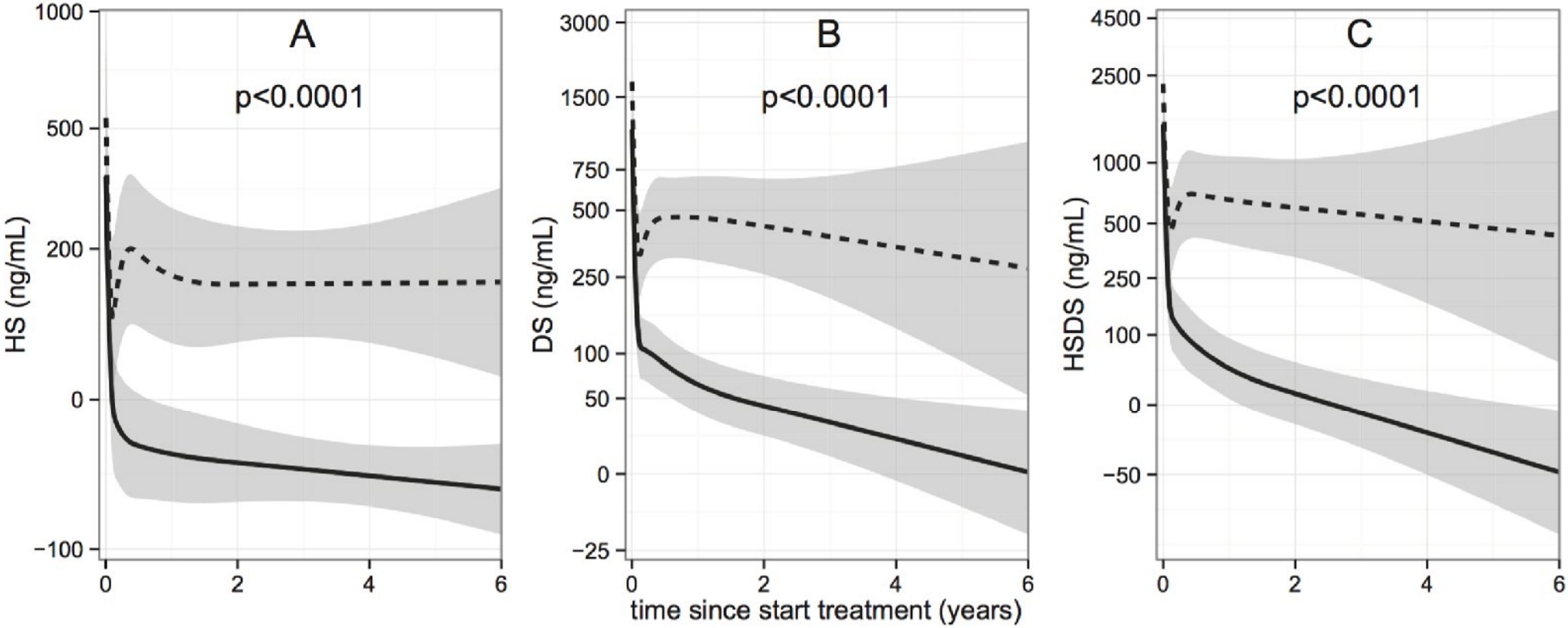


Saif (2012) Haematologica ;97(9):1320-1328

Uptake inhibitory antibodies correlate with a poorer reduction in biomarkers

Biomarker responses correlate with antibody status in mucopolysaccharidosis type I patients on long-term enzyme replacement therapy

Eveline J. Langereis [a], Naomi van Vlies [a,b], Heather J. Church [c], Ronald B. Geskus [d], Carla E.M. Hollak [e], Simon A. Jones [c], Wim Kulik [b], Henk van Lenthe [b], Jean Mercer [c], Lena Schreider [f], Karen L. Tylee [c], Tom Wagemans [a,b], Frits A. Wijburg [a,*], Brian W. Bigger [f]

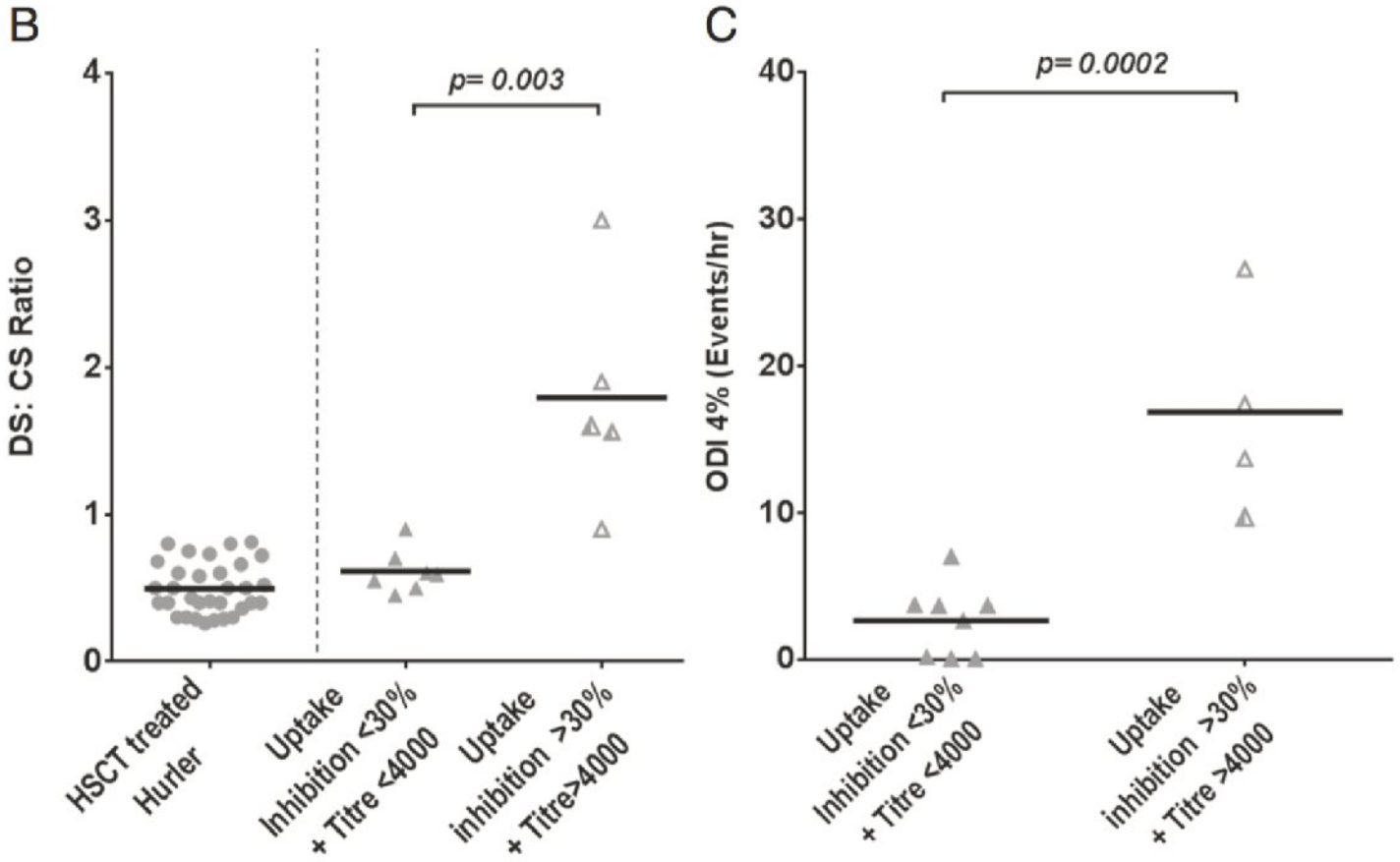


Langereis (2014), Mol Genet Metab

Uptake inhibition correlates with presence and severity of sleep disordered breathing

Sleep disordered breathing in mucopolysaccharidosis I: a multivariate analysis of patient, therapeutic and metabolic correlators modifying long term clinical outcome

Abhijit Ricky Pal[1,2], Eveline J Langereis[3], Muhammad A Saif[2,4], Jean Mercer[5], Heather J Church[5], Karen L Tylee[5], Robert F Wynn[4], Frits A Wijburg[3], Simon A Jones[5], Iain A Bruce[1] and Brian W Bigger[2*]



Pal (2015), Orphanet J Rare Dis

Biomarkers in LSDs

- Gaucher: Chito, ACE, PARK
- Fabry: urine Gb3, plasma lyso Gb3
- Pompe: urine hex4
- Mannosidosis: mannose
- MPS: urine GAGs:
  - Total
  - 2D electrophoresis
  - DS/CS ratios
  - Direct GAG measures (mostly MS/MS)

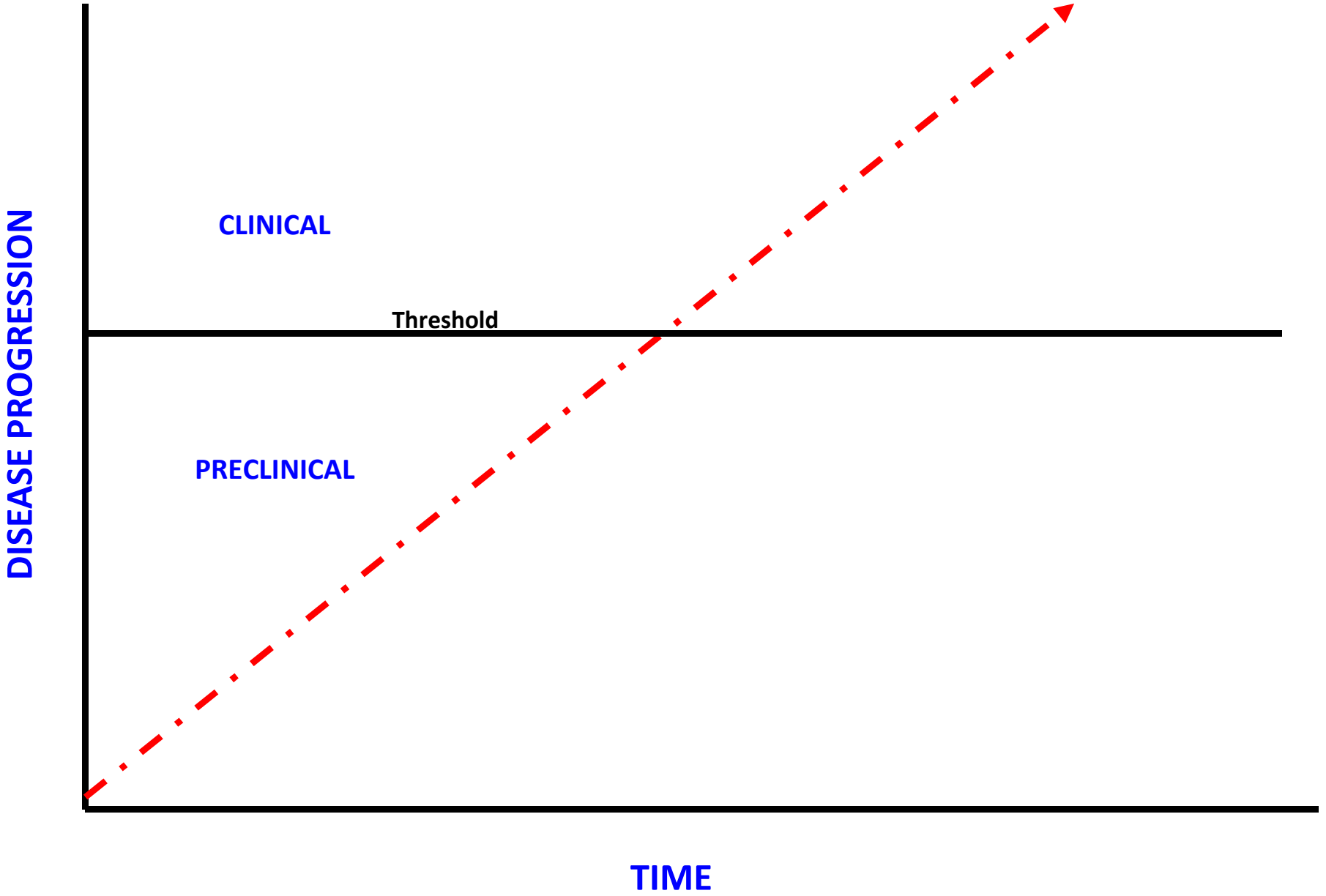
Biomarkers in LSDs

- What is the purpose?
  - Screening tests to aid diagnosis
  - Phenotyping
  - Clinical trials (PD)
  - Monitoring treatment – why?
    - Ensure compliance?
    - Guiding dosing/treatment decisions?
    - Detection of antibodies?

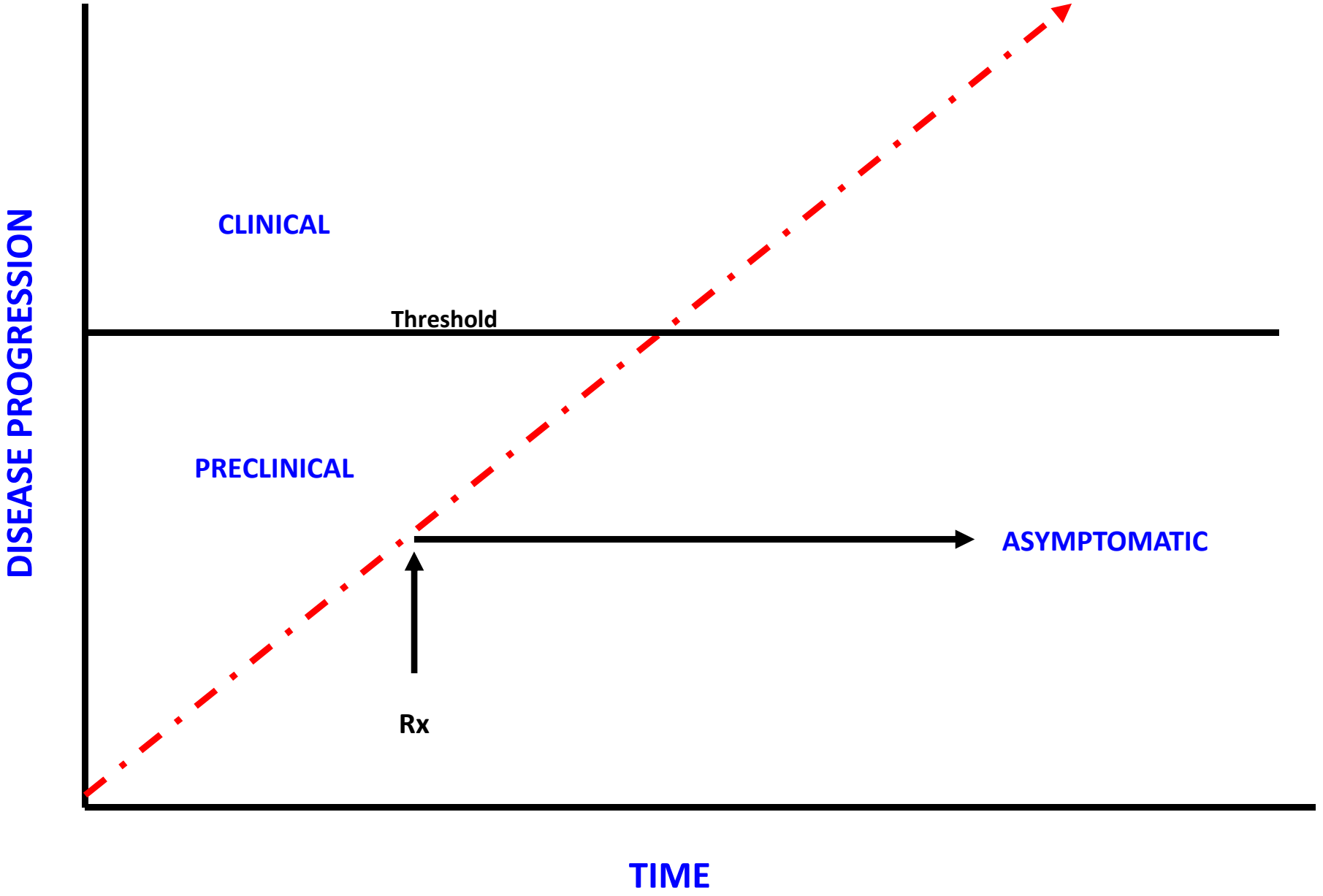
Biomarkers in LSDs

- Do we make treatment decisions based on biomarkers?
- If not then why not?
- How can we do better?
  - More sensitive and specific tests
  - Predictive value
  - Clinical relevance of the change in biomarker

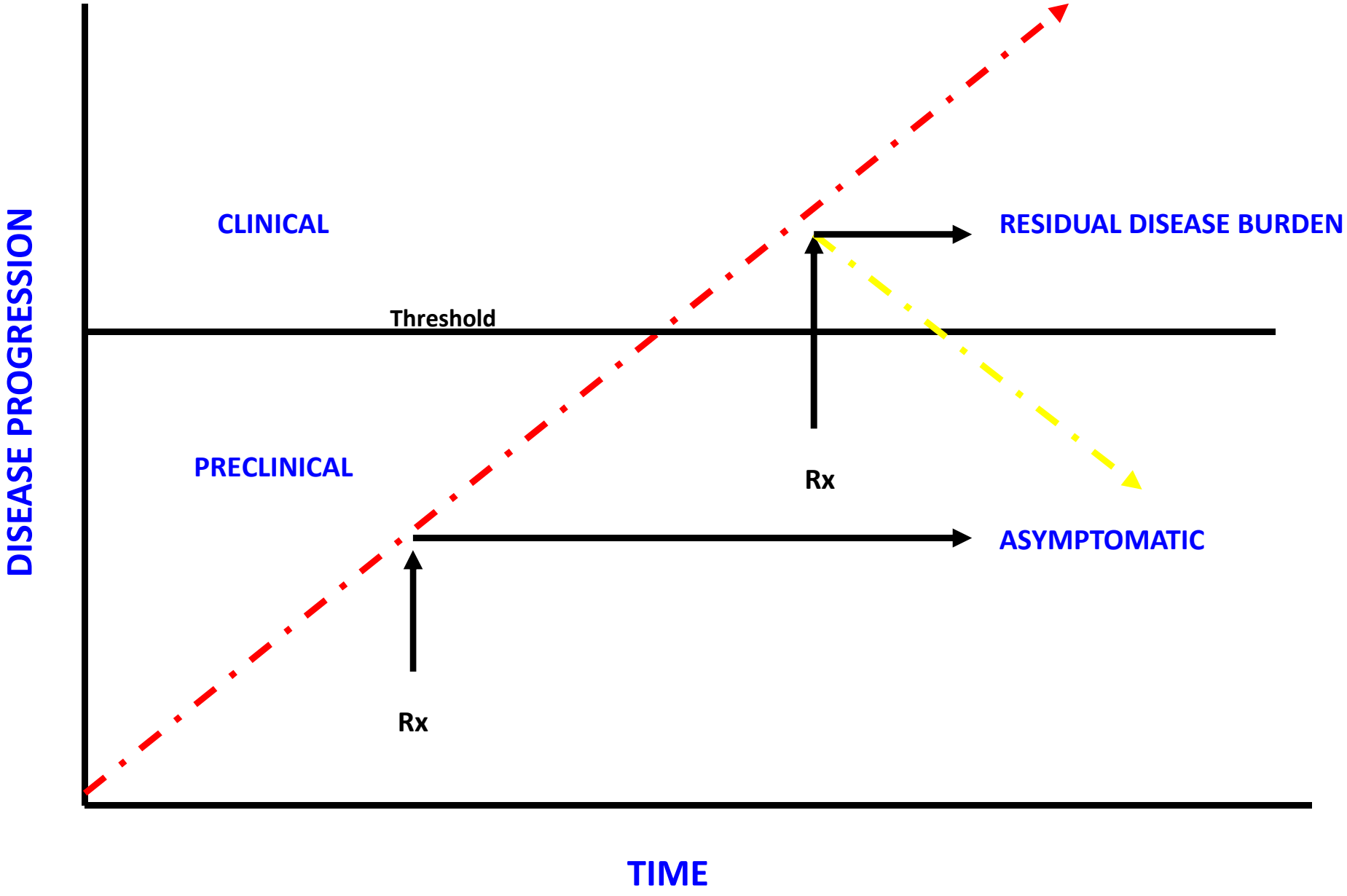
Disease Progression



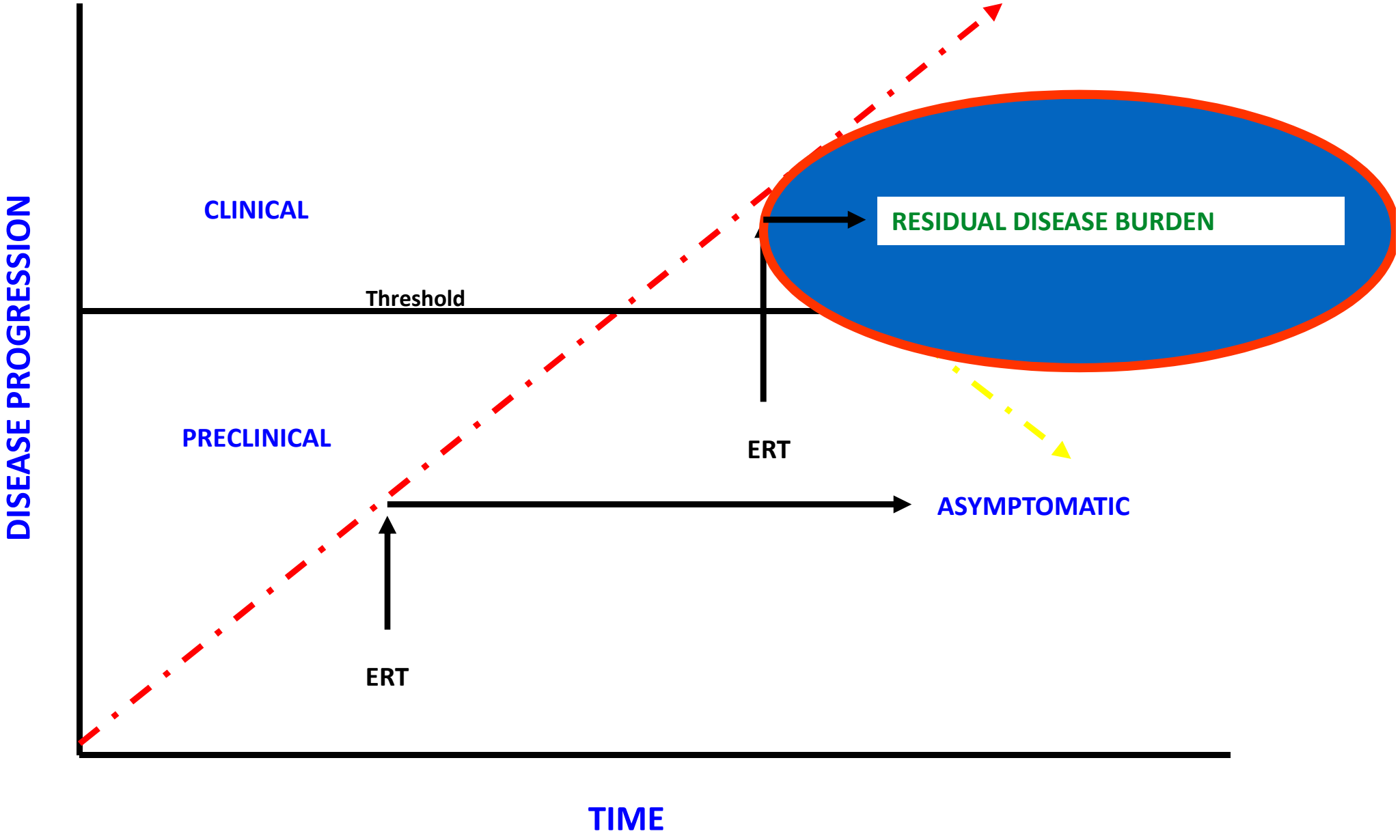
Therapeutic response to Rx



Therapeutic response to Rx



Therapeutic response to ERT



Conclusions

- There are many treatments for LSDs now with many more to come
- The CNS will be a major target organ
- Development of biomarkers and understanding their clinical relevance will become a critical part of this
- Laboratory/clinical collaboration essential to this venture, and numbers of patients/ samples required mandates multi-centre working

Acknowledgements

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- Willink Unit clinical and laboratory team
- Rob Wynn

- Brian Bigger (UoM)
- AMC (FW and FV)
- UK MPS society
- GEM appeal