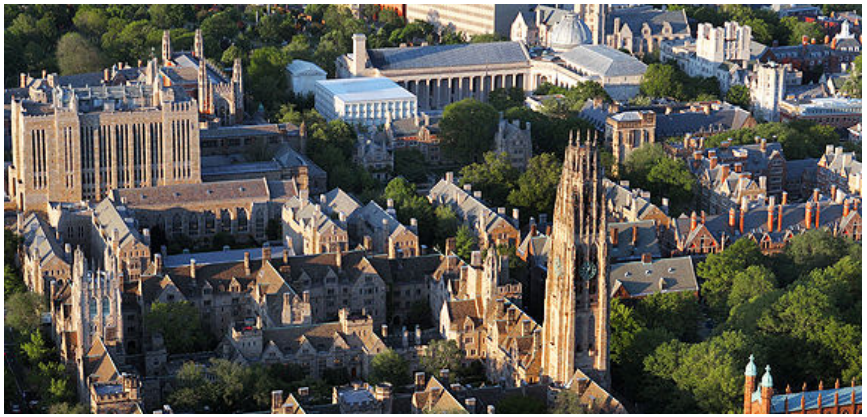
2019 Update in Neuronopathic GD



Pramod K Mistry, MD, PhD,
Professor of Medicine and Pediatrics

National Gaucher Foundation

Annual NYC Meeting,
Museum of the City of New York
October, 29, 2017

Disclosures

- Received research funding from
  - NIH R01/K24
  - Gaucher Generation Program Senior Investigator Award
  - National Gaucher Foundation
  - Sanofi Genzyme, a Center of Excellence for Treatment of Gaucher Disease
  - Shire
- Travel support and honoraria from Genzyme, Pfizer and Shire
- Chair of the Project Hope Humanitarian Program for Gaucher disease
- Chair of the International Gaucher Registry, ICGG

Update in Type 3 Gaucher disease - 2017

- Important global disease
- Long-term response to enzyme replacement therapy
- Unmet needs:
    - remains a disabling and life-threatening disease
    - lung disease
    - spinal deformity
    - abdominal lymphadenopathy
    - neurological signs
- New clinical trial of brain-penetrant SRT

Gaucher Disease Classifications

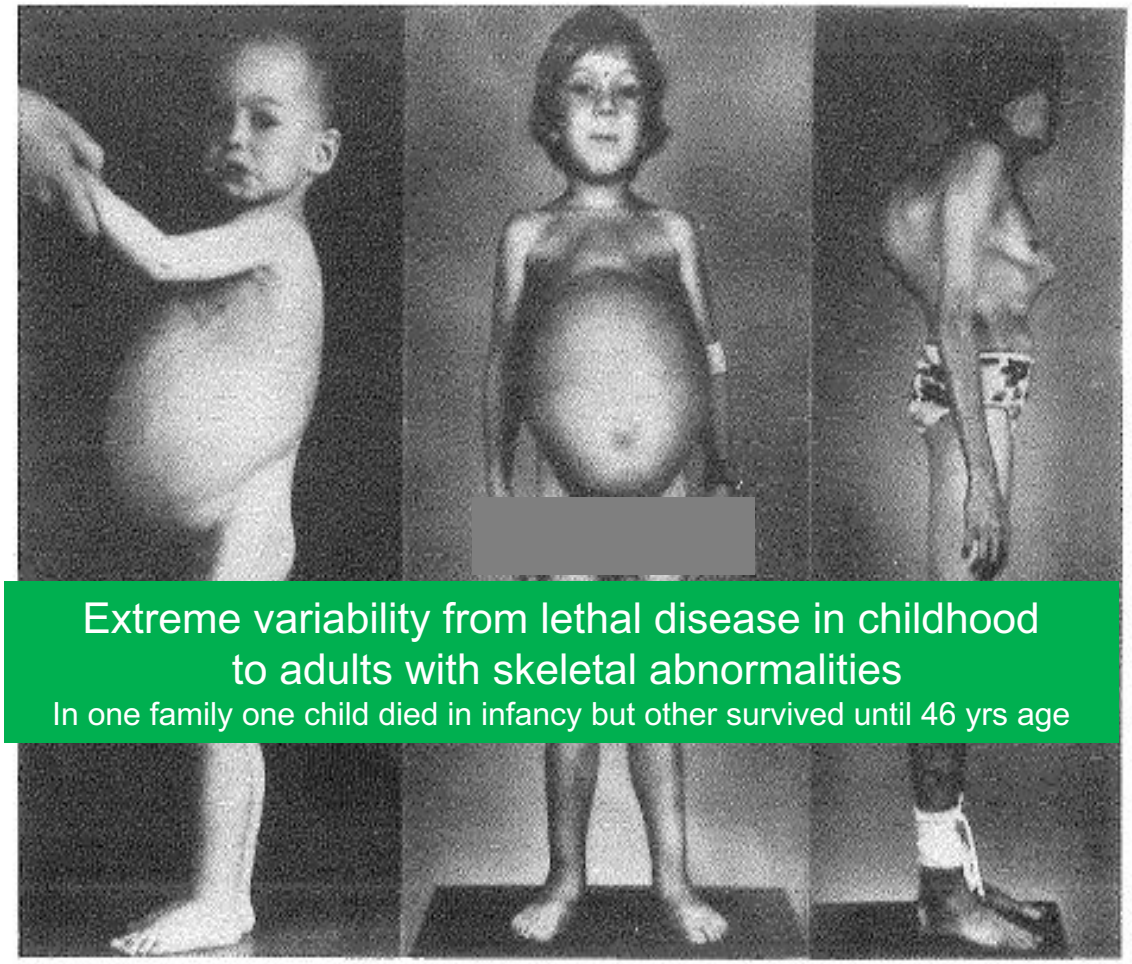
Type 1 (nonneuronopathic)	**Type 2** (acute neuronopathic)	**Type 3** (chronic neuronopathic)
Panethnic (~1:60,000) Prevalent in Ashkenazi Jews (~1:850) Onset in childhood or adulthood	Panethnic (~1:100,000) Onset in infancy, death < 2 years	Panethnic (~1:100,000) Onset in childhood

Weiss K et al, Mol Genet Metab, 2015
Sidransky E. Mol Genet Metab. 2004;83:6-15.

Story of GD3 began in Northern Sweden – First cluster of GD3 Described in Norbotten and Vasterbotten

Hillborg and Svennerholm, Acta Paeditrica,1960

First descriptions of Gaucher disease in Norrbotten
-Severe life-threatening disease starting in childhood
- severe liver/spleen enlargement, low blood counts, growth failure
- and neurological symptoms

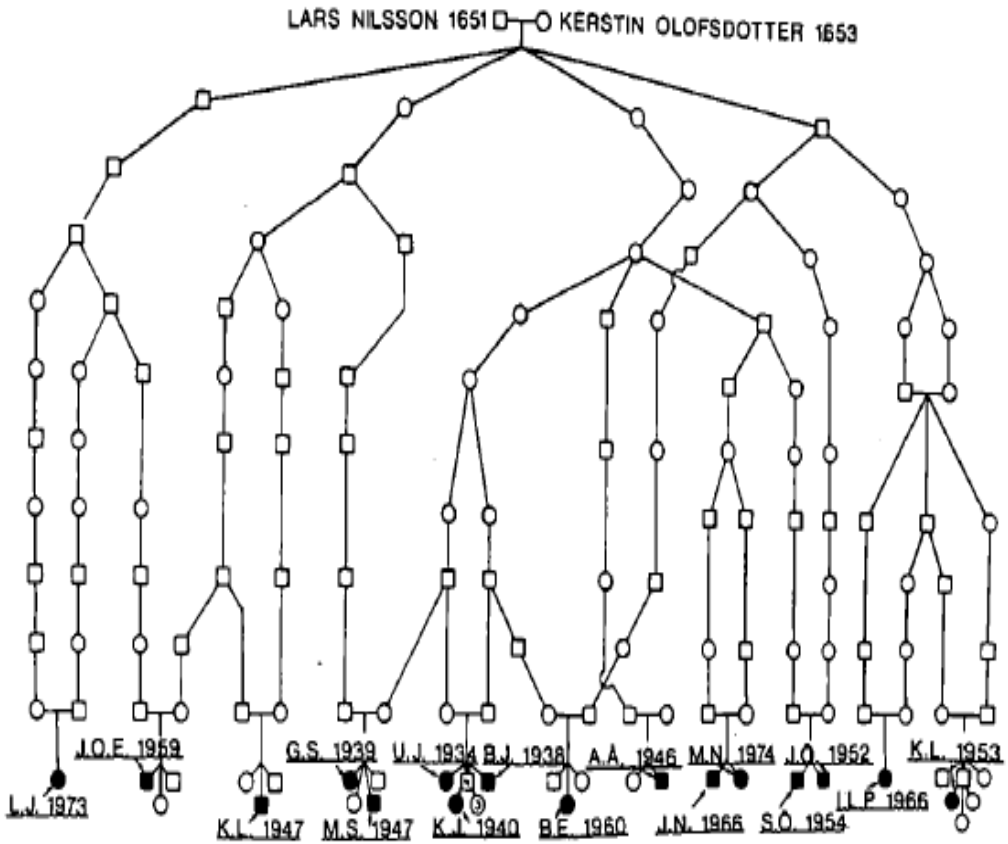


Extreme variability from lethal disease in childhood to adults with skeletal abnormalities

In one family one child died in infancy but other survived until 46 yrs age

Svennerholm L et al, 1982, Progr in Biol Res

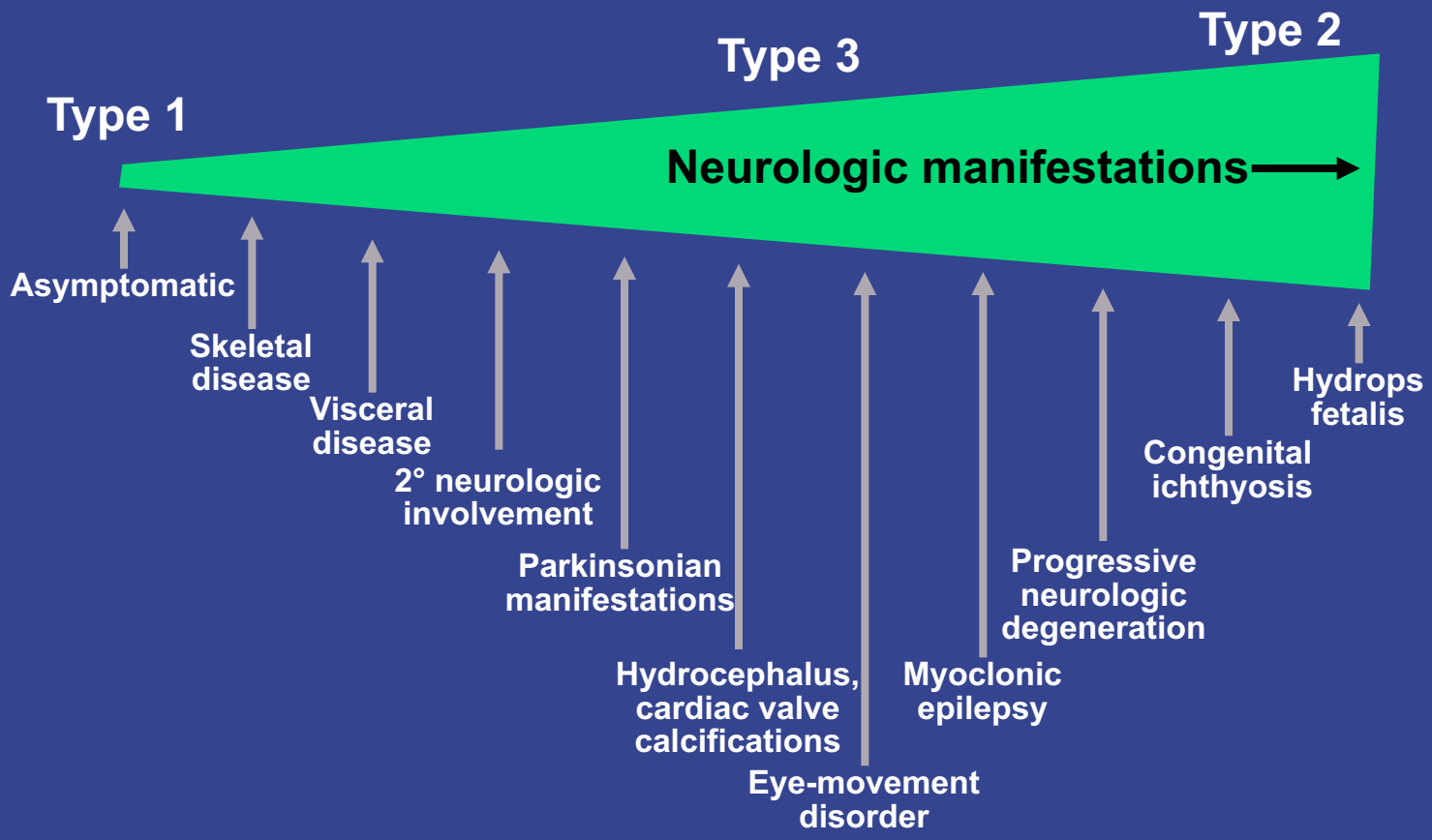
Pedigree for Norrbotten branch of Gaucher disease
All GD3 patients (filled circles) descended from common ancestors
Yet, highly variable disease severity



Several groups working to identify modifiers that lead to variable severity

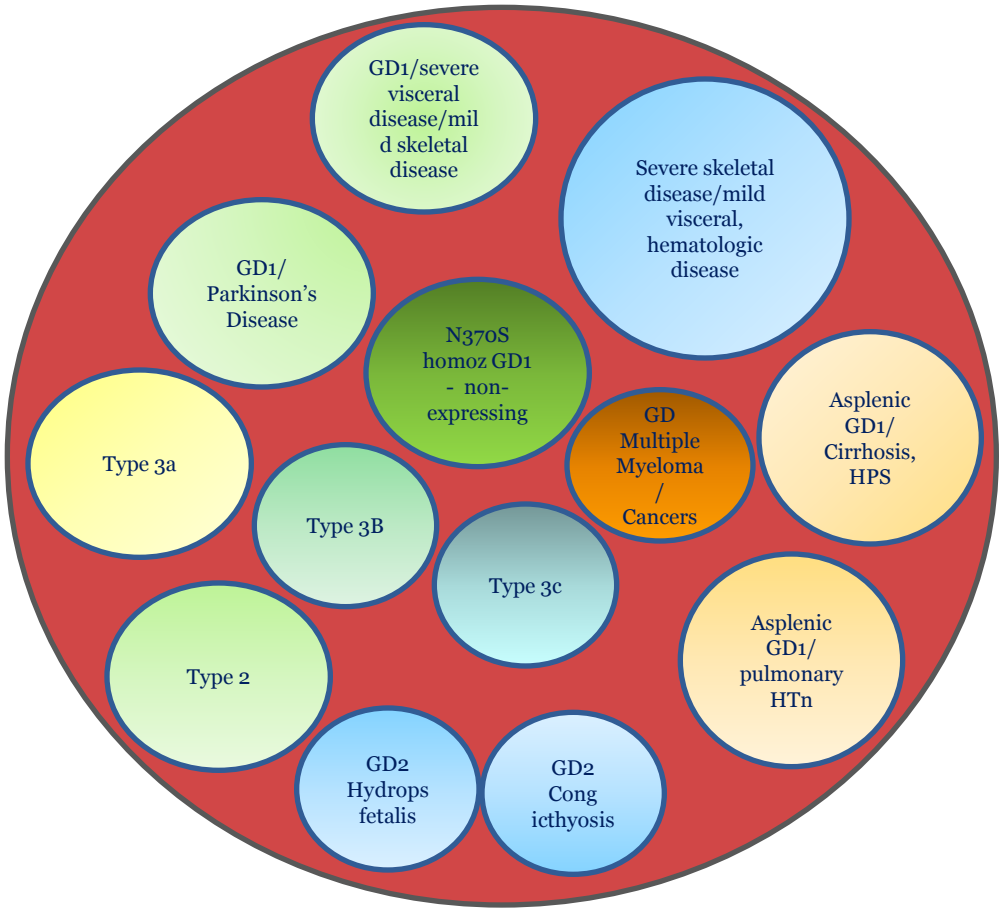
Svennerholm L et al, 1982

Phenotype Continuum



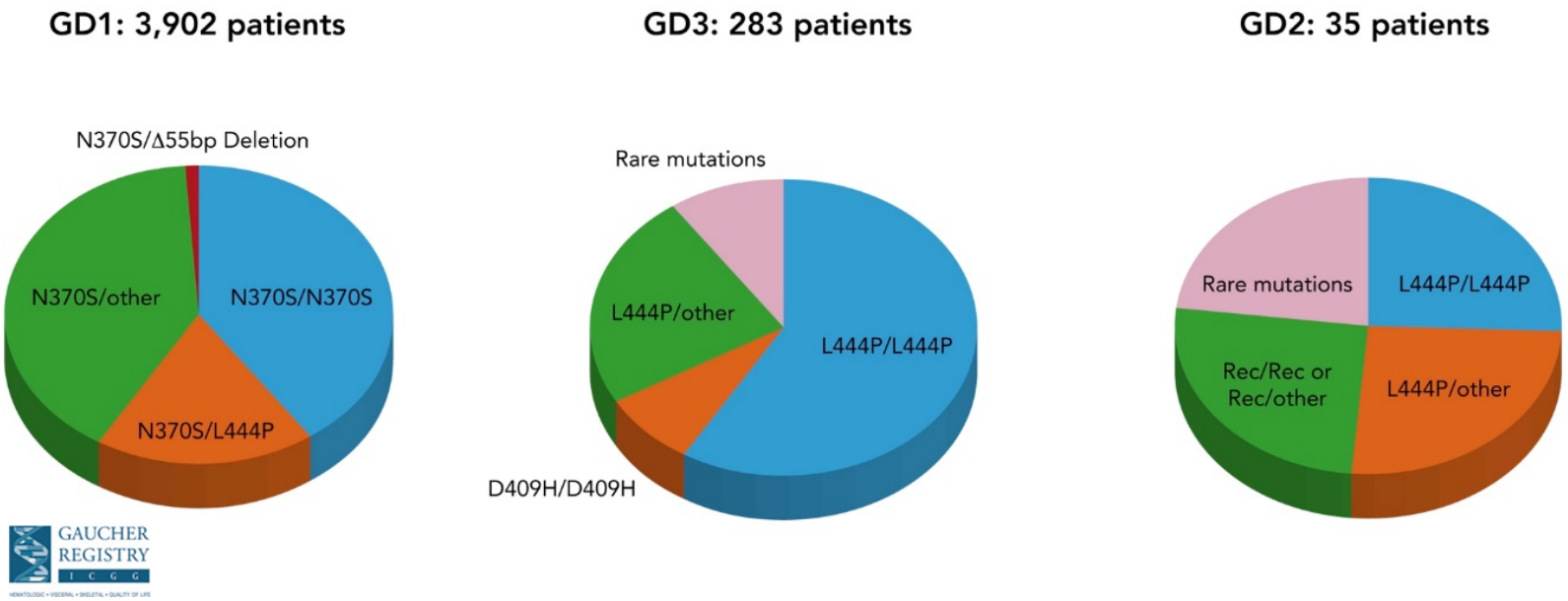
Sidransky E. *Disco Med*. 2012;14:273-81;
Sidransky E. *Mol Genet Metab*. 2004;83:6-15.

Multiple syndromes of GD due to single gene, single enzyme deficiency



Global distribution of GBA genotypes by phenotype in ICGG Registry

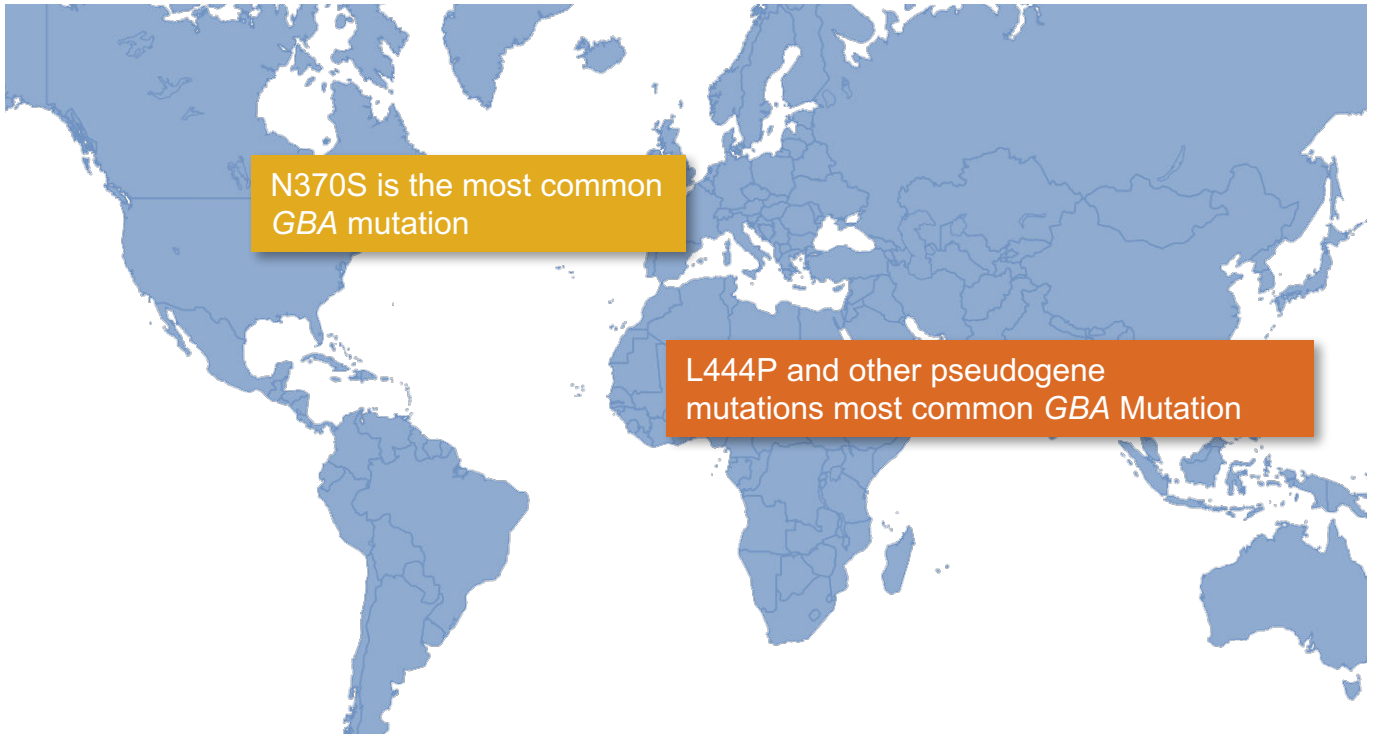
Presence of at least one N370S allele precludes neuronopathic GD



ClinicalTrials.gov NCT00358943

Am J Hematol. Suppl to Celebrate 20th anniversary of ICGG 2015 Jul;90 Suppl 1:S12-8.

Global distribution of Gaucher disease mutations



Neuronopathic Gaucher disease (NGD) is rare: ~1 in 100,000 individuals
However, world-wide, there are many more NGD patients than GD1
Worldwide prevalence varies substantially
- US, Europe and Israel: 5% of GD patients classified as GD3 and 1% as GD2
- Egypt, Korea, Taiwan, and China: at least one-third of GD patients classified as GD3 or GD2

Two ICGG Gaucher Registry* Studies of Neuronopathic Gaucher Disease (NGD)

Largest cohorts of NGD studied to date

Neurological Outcomes Subregistry [1]	GD3 Treated with Imiglucerase Starting <18 Years Old[2]
• N=131 • Initiated in 2004, captured full worldwide spectrum of NGD • All patients in ICGG Registry with confirmed GD diagnosis and neurologic manifestations • Baseline: data point closest to diagnosis date within ±2 years • Data analysis: patients enrolled in the Subregistry as of 1 June 2007	• N=253 • All GD3 patients in the ICGG Registry as of 4 September 2015 who started alglucerase/imiglucerase at <18 years of age • Baseline: value closest to treatment initiation up to 2 wks after • Data analysis: annually from baseline through treatment year 5

*ICGG Registry: International Collaborative Gaucher Group Gaucher Registry

Tylki-Szymanska A, et al. *J Inherit Metab. Dis*. 2010;33(4):339-46.
El-Beshlawy A, et al. Mol Genet Metab. 2017 Jan - Feb;120(1-2):47-56

GAUCHER REGISTRY ICGG

NGD Demographics and Clinical Characteristics in the ICGG Registry

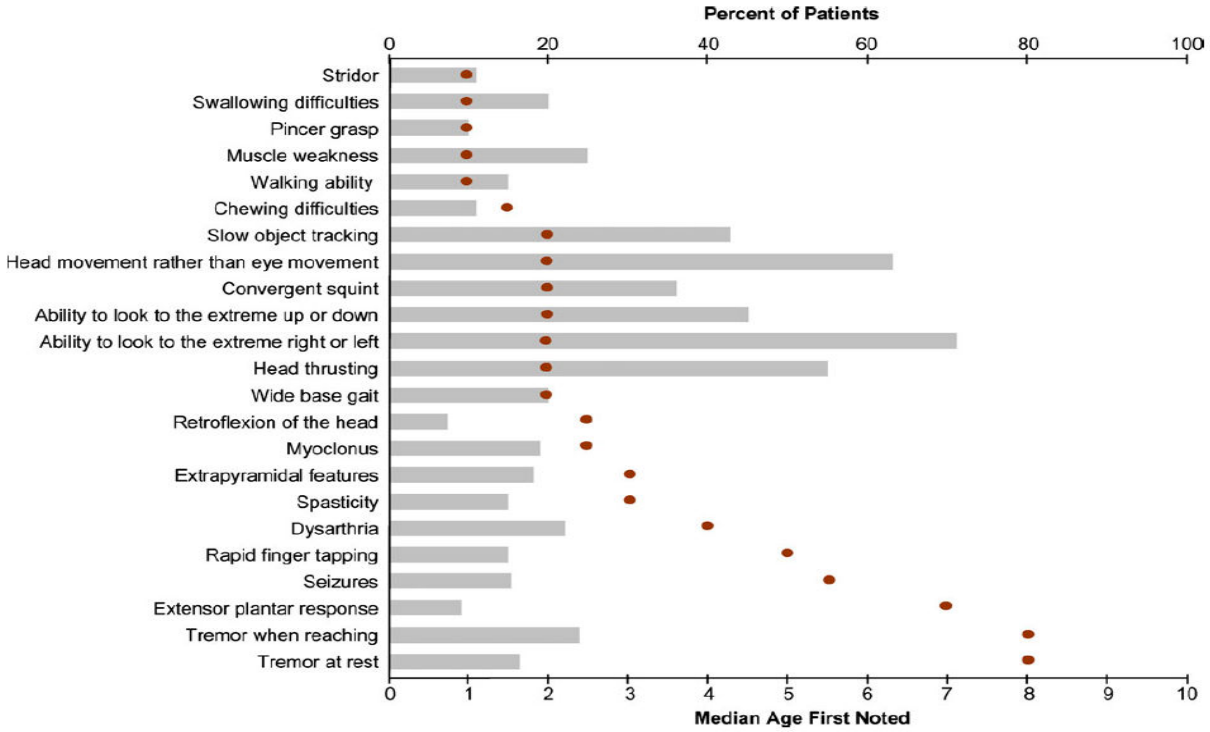
Parameter	Neurological Outcomes Sub-registry (2010)[1] N=131	GD3 Patients Started on Imiglucerase <18 years Old (2016)[2] N=253
Gender, n (%)		
Male	61 (47%)	126 (49.8%)
Female	70 (53%)	127 (50.2%)
Age at GD Diagnosis (Years)		
Mean (SD)	3.2 (6.2)	2.7 (2.81)
Median (min, max)	1.0	1.7 (0.0, 16.7)
Age of onset of Neurological Manifestations, n (%)		
< 2 years	61 (47%)	57%
≥ 2 years	54 (41%)	NR
Unknown	16 (12%)	NR

Neurological manifestations often appear before 2 years of age.

1. Tylki-Szymanska A, et al. *J Inherit Metab. Dis*. 2010;33(4):339-46.
2. *El-Beshlawy A, et al. Mol Genet Metab. 2017 Jan - Feb;120(1-2):47-56*

GAUCHER REGISTRY ICGG

NGD Neurologic Manifestations:
Neurological Outcomes Sub-registry



The most common neurological signs and manifestations are brainstem abnormalities and fine motor dysfunction.

Tylki-Szymanska A et alJ Inherit Metab. Dis. 2010;33(4):339-46.

Natural Course of Neuronopathic Manifestations in Gaucher Disease

Birth-2 years

- Visceral disease
- Stridor
- Swallowing difficulties
- Pincer grasp
- Muscle weakness
- Walking ability (needs assistance/ non-ambulatory)
- Chewing difficulties
- Slow object tracking
- Head movement rather than eye movement
- Convergent squint
- Ability to look to extreme up or down
- Ability to look to extreme left or right
- Head thrusting
- Wide base gait

2-5 years

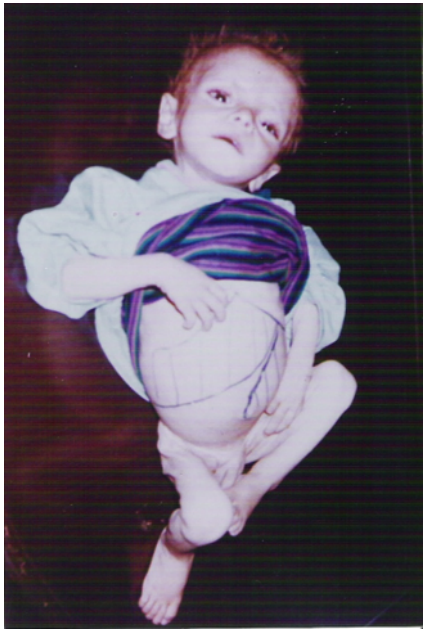
- Retroflection of head
- Myoclonus
- Extrapyramidal features
- Spasticity
- Dysarthria
- Rapid finger tapping

5-10 years

- Seizures
- Extensor plantar response
- Tremor when reaching
- Tremor at rest

Age of onset of Neurological Manifestations (N=131)	
<2 years	61 (47%)
≥2 years	54 (41%)

Devastating visceral and hematologic disease with growth failure in GD3



Parameters	Baseline
Hemoglobin (g/dL), mean (SD)	**9.6** (1.92) *n=163*
Platelet Count (x10^9/L), mean (SD)	**127.4** (99.24) *n=161*
Liver Volume (MN), mean (SD)	**2.4** (1.28) *n=49*
Spleen Volume (MN), mean (SD)	**34.6** (15.26) *n=63*
Height Z-Score, mean (SD)	**-1.8** (1.43) *n=140*

El-Beshlawy A, et al. Mol Genet Metab. 2017 Jan - Feb;120(1-2):47-56

Imiglucerase Improves Hematologic, Visceral and Growth Outcomes in children with GD3

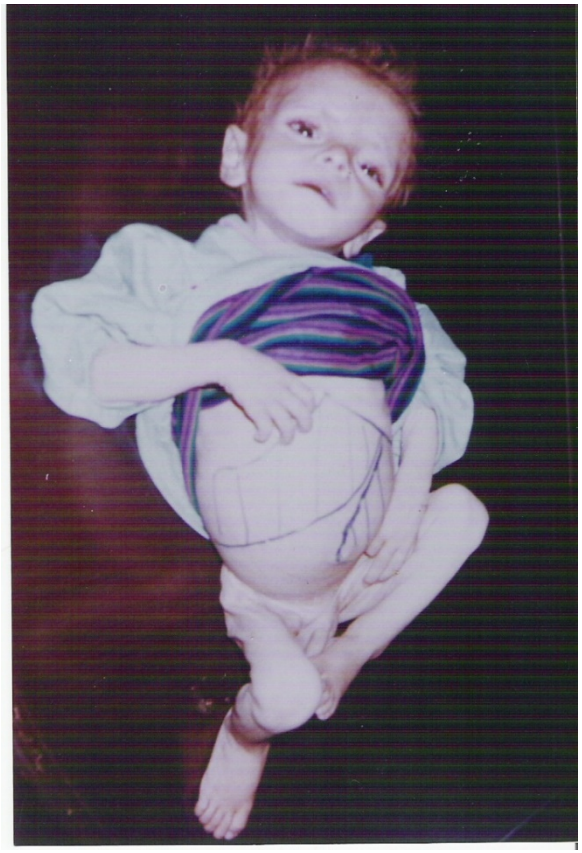
ICGG Registry, Started Imiglucerase <18 Years of Age

Parameters	Baseline	Years on ERT				
		>0 to ≤1	>1 to ≤2	>2 to ≤3	>3 to ≤4	>4 to ≤5
Hemoglobin (g/dL), mean (SD)	**9.6** (1.92) *n=163*	**11.4** (1.68) *n=143*	**11.7** (1.52) *n=125*	**11.8** (1.57) *n=113*	**12.1** (1.57) *n=95*	**12.0** (1.46) *n=96*
Platelet Count (x10^9/L), mean (SD)	**127.4** (99.24) *n=161*	**182.0** (94.32) *n=139*	**212.5** (89.86) *n=123*	**226.6** (97.19) *n=111*	**219.5** (90.69) *n=92*	**218.0** (79.60) *n=95*
Liver Volume (MN), mean (SD)	**2.4** (1.28) *n=49*	**1.7** (0.80) *n=33*	**1.4** (0.31) *n=34*	**1.2** (0.27) *n=31*	**1.3** (0.67) *n=27*	**1.2** (0.33) *n=25*
Spleen Volume (MN), mean (SD)	**34.6** (15.26) *n=63*	**23.3** (12.29) *n=43*	**20.7** (11.41) *n=44*	**15.7** (7.25) *n=39*	**14.3** (6.93) *n=35*	**11.9** (5.86) *n=33*
Height Z-Score, mean (SD)	**-1.8** (1.43) *n=140*	**-1.6** (1.43) *n=118*	**-1.5** (1.37) *n=103*	**-1.2** (1.24) *n=93*	**-1.2** (1.16) *n=85*	**-1.2** (1.20) *n=82*

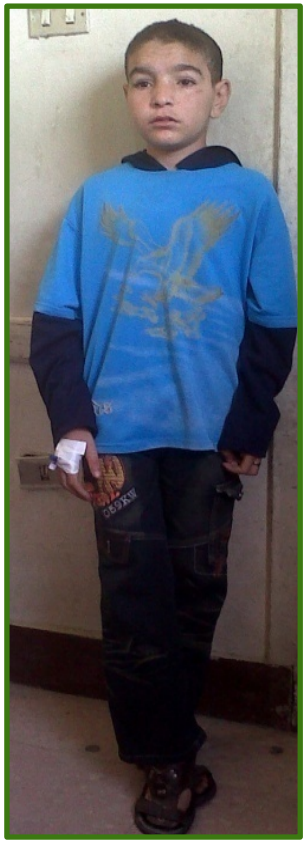
El-Beshlawy A, et al. Mol Genet Metab. 2017 Jan - Feb;120(1-2):47-56

GAUCHER REGISTRY ICGG

Type 3 Gaucher disease: Response to ERT



At Diagnosis

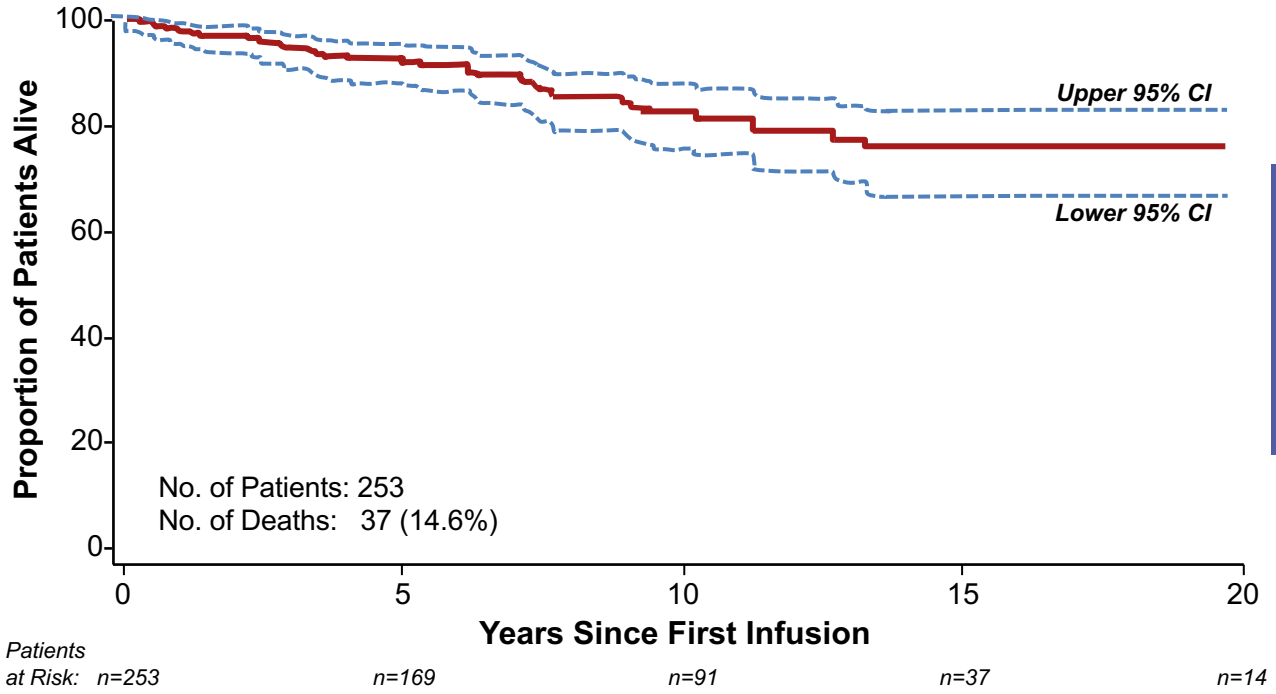


Age 14 on imiglucerase ERT

With permission Dr El-Beshlawy

High Survival Probability with Imiglucerase in children life-threatening visceral/hematologic disease

ICGG Registry, Started Imiglucerase <18 Years of Age



Probability of survival after starting imiglucerase:

5 years: 92%
10 years: 82%
20 years: 76%

GAUCHER REGISTRY ICGG

El-Beshlawy A, et al. Mol Genet Metab. 2017 Jan - Feb;120(1-2):47-56

Unmet needs in GD3

- Neurologic disease
- Lung involvement
- Abdominal lymphadenopathy
- Spinal deformity
- Cardiac involvement (in Type 3c)

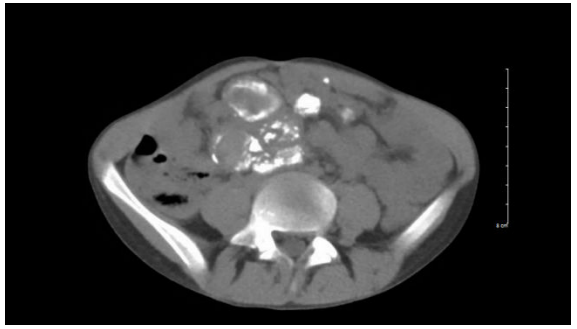
- Steve H
- Now 10 yrs old
- Diagnosed with GD3 at age 3,
  - Massive HSM
  - L444P/L444P
- On cerezyme since age 3
- IQ>130
- Doing Singapore math
- ADHD/autism

October 28, 2017

With permission Diana and Steven H

Tylan, now age 12
Genotype L444P/L444P
Massive liver/spleen enlargement, FTT,
low blood counts
Started enzyme treatment age 2 in 2006
For past 2 years FTT again

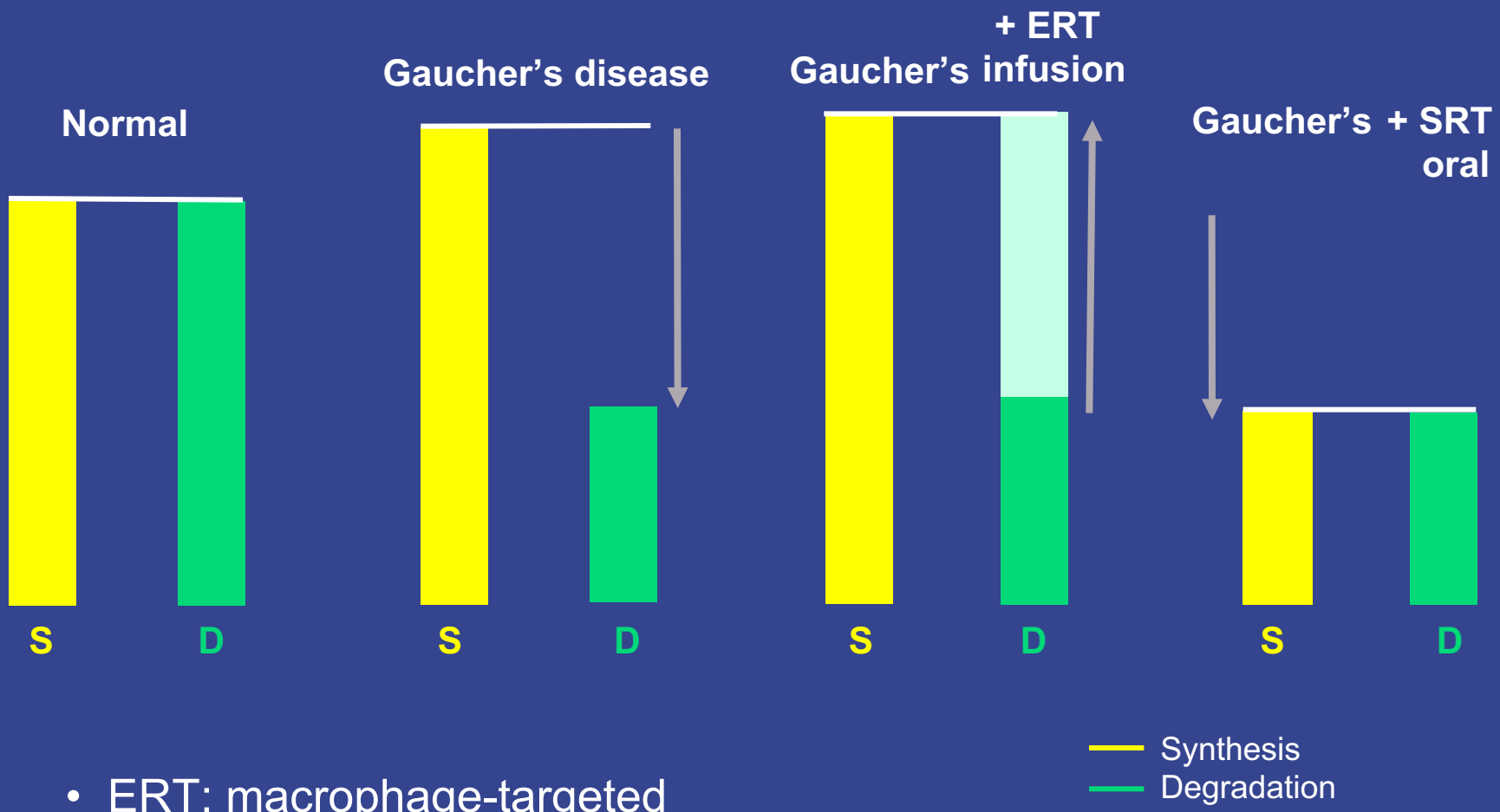
Massive abdominal lymphadenopathy
With duodenal obstruction



With permission Tiffany and Tylan C

Enzyme Replacement Therapy vs. Substrate Reduction Therapy

Synthesis (S) and degradation (D) of glucosylceramide



- ERT: macrophage-targeted
- SRT: affects all cell types

Bennett LL, et al. *Ann Pharmacother*. 2013;47:1182-93;
Rosenbloom BE, et al. *Crit Rev Oncog*. 2013;18:163-75.

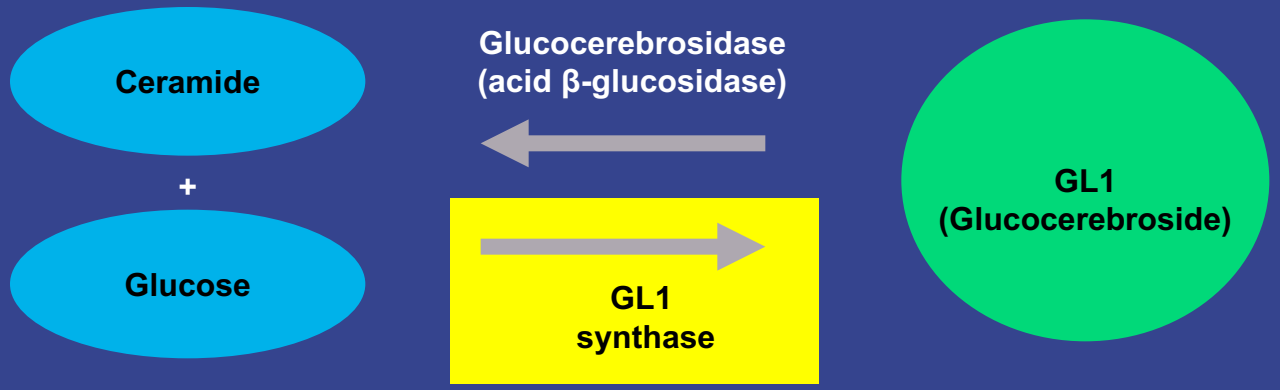
Inflammation at the center of GD

- Inflammation is central to all types of GD
  (Dr Grabowski's key note lecture)
- Inflammation increases GCS enzyme activity that is involved in formation of Gaucher lipids
- This amplifies GD defect of decreased breakdown of glucosylceramide

Therapeutic Targets in GD: Synthesis and Degradation of GL1

SRT: Oral Treatment With GL1 Synthase Inhibitors to Correct System-Wide Metabolic Abnormality

- Reduces GL1 by partial inhibition of its synthesis



Miglustat
IC_{50} 20-50 µM

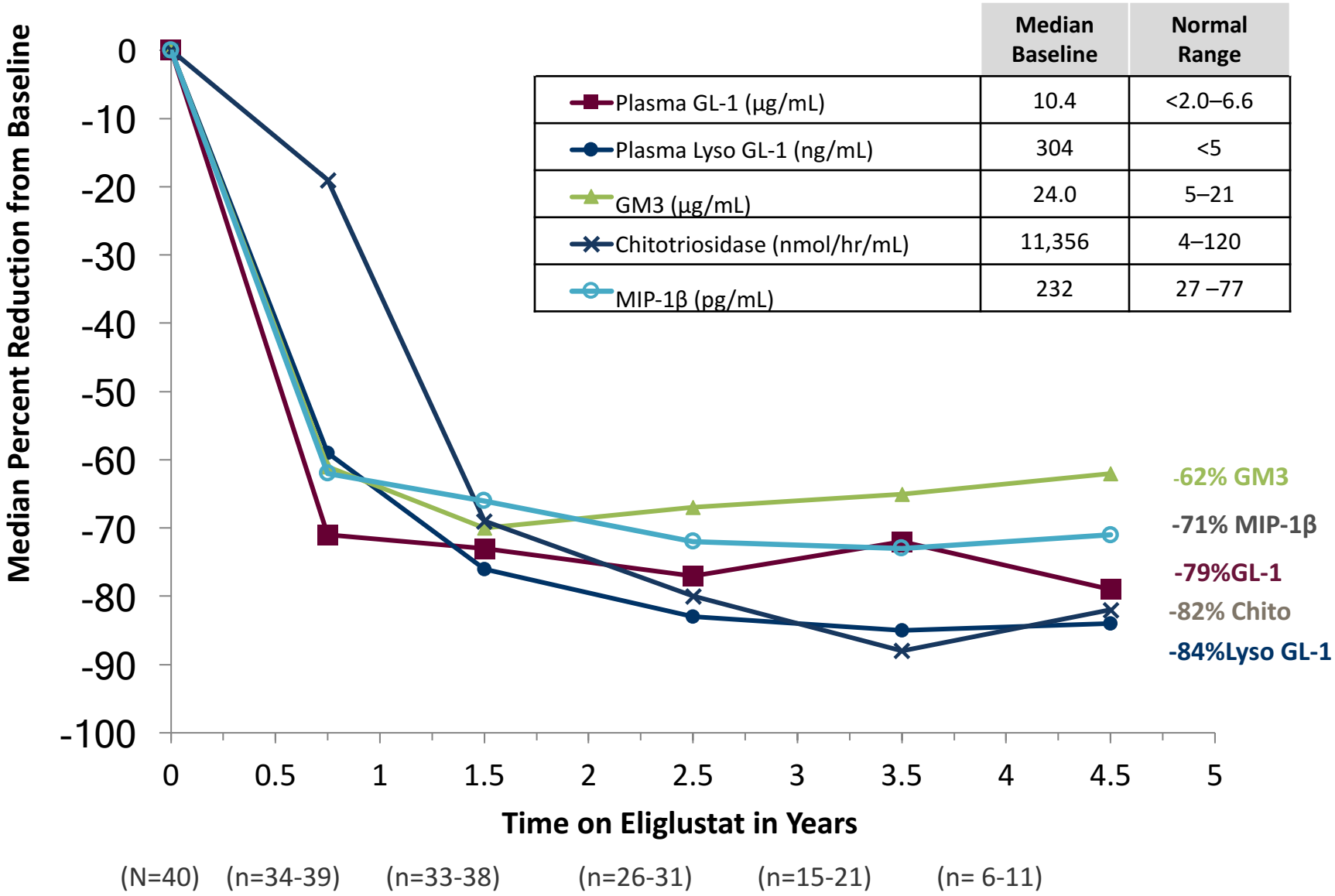
IC_{50} for GBA2: 0.31 µM

Eliglustat
IC_{50} 0.024 µM

IC_{50} for GBA2: 1600 µM

Shayman JA and Larsen SD, J Lipid Res, 2014, 55: 1255-225; Shayman JA, Trans Am Clin Climatol Assn, 2013, 124: 46-60 EMEA Scientific Discussion Zavesca, 2002, www.ema.europa.eu ; Platt FM and Jeyakumar M, Acta Paediatric Suppl, 2008, 97: 88-93 McEachem EA et al, Mol Genet Metab, 2007, 9: 259-67

ENGAGE cerdelga trial: Decrease in inflammatory lipids and markers of inflammation



	Median Baseline	Normal Range
Plasma GL-1 (µg/mL)	10.4	<2.0–6.6
Plasma Lyso GL-1 (ng/mL)	304	<5
GM3 (µg/mL)	24.0	5–21
Chitotriosidase (nmol/hr/mL)	11,356	4–120
MIP-1β (pg/mL)	232	27 –77

(N=40) (n=34-39) (n=33-38) (n=26-31) (n=15-21) (n= 6-11)

Mistry et al. WORLD 2017 presentation

Randomized, Controlled Trial of Miglustat in Gaucher's Disease Type 3

Raphael Schiffmann, MD,[1] Edmond J. FitzGibbon, MD,[2] Chris Harris, PhD,[3] Catherine DeVile, MD,[4] Elin H. Davies, MSc,[4] Larry Abel, PhD,[5] Ivo N. van Schaik, MD,[6] William S. Benko, MD,[1] Margaret Timmons, MD,[1] Markus Ries, MD, PhD, MHSc, FCP,[1] and Ashok Vellodi, FRCPCH[4]

Interpretation: Miglustat does not appear to have significant benefits on the neurological manifestations of GD3. However, miglustat may have positive effects on systemic disease (pulmonary function and chitotriosidase activity) in addition to ERT in patients with GD3.

Ann Neurol 2008;64:514–522

Limitations of current ERT and SRTs in GD3

- ERTs: most uptake in the liver, spleen and bone marrow, none in the brain
- SRTs: no neurological improvement

- Need next generation CNS penetrant SRT

Official journal of the American Society of Gene & Cell Therapy

MTOpen

original article

CNS-accessible Inhibitor of Glucosylceramide Synthase for Substrate Reduction Therapy of Neuronopathic Gaucher Disease

John Marshall[1], Ying Sun[2,3], Dinesh S Bangari[1], Eva Budman[1], Hyejung Park[1], Jennifer B Nietupski[1], Amy Allaire[1], Mary A Cromwell[1], Bing Wang[1], Gregory A Grabowski[2,3], John P Leonard[1] and Seng H Cheng[1]

[1]Sanofi Genzyme, Framingham, Massachusetts, USA; [2]Division of Human Genetics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; [3]Department of Pediatrics, University of Cincinnati School of Medicine, Cincinnati, Ohio, USA.

Treatment of mouse models of nGD

- Reduced Gaucher lipids
- Reduced neurological symptoms
- Improved survival

LEAP trial : GZ/SAR402671 in Combination With Cerezyme in Adult Patients Wit h Gaucher Disease Type 3

Purpose Primary Objective:

Part 1:

- Evaluate central nervous system (CNS) biomarkers in adult GD3 patients that distinguish GD3 from GD1.
- Screen adult GD3 who qualify for treatment with GZ/SAR402671 in Part 2.

Part 2:

- Evaluate the safety and tolerability of GZ/SAR402671 in adult GD3.
- Evaluate the change in cerebrospinal fluid (CSF) central nervous system, biomarkers from adult GD3 receiving GZ/SAR402671.

Secondary Objectives:

- Evaluate the pharmacokinetics of GZ/SAR402671 in adult GD3.
- Explore the efficacy of GZ/SAR402671 in infiltrative lung disease in adult GD3
- Explore the efficacy of GZ/SAR402671 in systemic disease in adult GD3.
- Explore the efficacy of GZ/SAR402671 in neurological function and on exploratory CSF biomarkers in adult GD3.

ClinicalTrials.gov Identifier: NCT02843035

Inclusion criteria

- Has a clinical diagnosis of GD1 or GD3
- Hemoglobin level of ≥11.0 g/dL for females and ≥12.0 g/dL for males.
- Platelet count ≥100 000/mm^3.
- Spleen volume <10 multiples of normal (MN).
- Liver volume <1.5 MN.
- No bone crisis and free of symptomatic bone disease such as bone pain attributable to osteonecrosis and/or pathological fractures within the last year.
- Received treatment with ERT for at least 3 years.
- Female of childbearing potential must have a negative pregnancy test
- If the patient has a history of seizures, except for myoclonic seizures, they are well controlled

Adult GD1 cohort only:

- -GD1 patient is ≥18 and ≤40 years of age.
- Adult GD3 cohort only:

GD3 patient is ≥18 years of age.

- Willing to abstain from consumption of grapefruit,
- Oculomotor apraxia characterized by a horizontal saccade abnormality.
- Cerezyme treatment every 2 weeks (minimum dose 30 U/kg every 2 weeks).
- Females of childbearing potential - effective methods of contraception.

ClinicalTrials.gov Identifier: NCT02843035

Exclusion criteria

- SRT or chaperone therapy for GD within 6 months prior to enrollment.
- splenectomy.
- The patient is blood transfusion-dependent.
- Severe liver , cardiac or renal disease
- history of cancer
- Has myoclonic seizures.
- Pregnant or lactating.
- Use of invasive ventilatory supporT
- Hypersensitivity to Cerezyme
- Has received strong or moderate inducers or inhibitors of CYP3A within 30 days or 5 half-lives from screening, whichever is longer, prior to enrolment in Part 2. This also includes the consumption of grapefruit, grapefruit juice, or grapefruit containing products within 72 hours of starting GZ/SAR402671 administratio
- Has had a major organ transplant (eg, bone marrow or liver).
- The patient is unable to adhere to the requirements of the study.

ClinicalTrials.gov Identifier: NCT02843035

Treatments under investigation

- Need to conduct proper clinical trials for maximum benefit for patients to assess safety and effectiveness.

Future options to watch out for nGD families

PNAS

Histone deacetylase inhibitors prevent the degradation and restore the activity of glucocerebrosidase in Gaucher disease

Jie Lu[a,1], Chunzhang Yang[a,1], Masako Chen[a], Donald Y. Ye[a], Russell R. Lonser[a], Roscoe O. Brady[b,2], and Zhengping Zhuang[a,2]

[a]Surgical Neurology Branch and [b]Developmental and Metabolic Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892-1414

Contributed by Roscoe O. Brady, November 22, 2011 (sent for review October 28, 2011)

NEURAL REGENERATION RESEARCH
November 2016, Volume 11, Issue 11

● PERSPECTIVE

Chaperoning glucocerebrosidase: a therapeutic strategy for both Gaucher disease and Parkinsonism

Benjamin McMahon, Elma Aflaki, Ellen Sidransky*

Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, USA

ANNALS of Clinical and Translational Neurology
Open Access
ANA American Neurological Association

RESEARCH ARTICLE

Ambroxol chaperone therapy for neuronopathic Gaucher disease: A pilot study

Aya Narita[1], Kentarou Shirai[1], Shinji Itamura[1], Atsue Matsuda[1], Akiko Ishihara[2], Kumi Matsushita[2], Chisako Fukuda[3], Norika Kubota[4], Rumiko Takayama[5], Hideo Shigematsu[5], Anri Hayashi[6], Tomohiro Kumada[6], Kotaro Yuge[7], Yoriko Watanabe[7], Saori Kosugi[8], Hiroshi Nishida[8], Yukiko Kimura[8], Yusuke Endo[9], Katsumi Higaki[10], Eiji Nanba[10], Yoko Nishimura[1], Akiko Tamasaki[1], Masami Togawa[1], Yoshiaki Saito[1], Yoshihiro Maegaki[1], Kousaku Ohno[1] & Yoshiyuki Suzuki[11]

Repeated-Dose Oral N-Acetylcysteine in Parkinson's Disease: Pharmacokinetics and Effect on Brain Glutathione and Oxidative Stress

The Journal of Clinical Pharmacology
2017, 00(0) 1–10
© 2017, The American College of Clinical Pharmacology
DOI: 10.1002/jcph.1008

Lisa D. Coles, PhD[1], Paul J. Tuite, MD[2], Gülin Öz, PhD[3], Usha R. Mishra, MS[1], Reena V. Kartha, PhD[1], Kathleen M. Sullivan, BS[1], James C. Cloyd, PharmD[1], and Melissa Terpstra, PhD[3]

National Gaucher Foundation

Dedicated to all Gaucher disease
For more than 3 decades

With permission Veronica H.

Thank you
Questions?