2ND SUMMIT RARE DISEASES COPAC

# Therapeutic Opportunities according to Therapeutic Objectives

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Hematologist
Ricardo Gutierrez Hospital

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MAT-CO-2202523 08/2022

# Declaración Conflicto de Interés

- He recibido honorarios por parte de Sanofi por esta conferencia.

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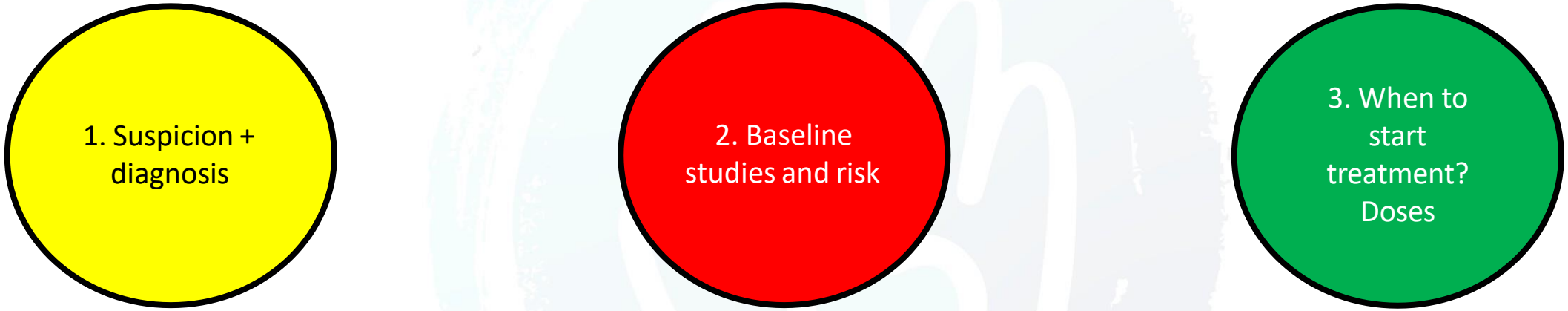
# AGENDA

**Therapeutic Opportunities according to therapeutic objectives in Gaucher Disease**

## Therapeutic opportunity =



# AGENDA

**Therapeutic Opportunities according to therapeutic objectives in Gaucher Disease**

**Therapeutic Objetives =**

5. Therapeutic Objetictives = Therapeutics Goals (TGs)

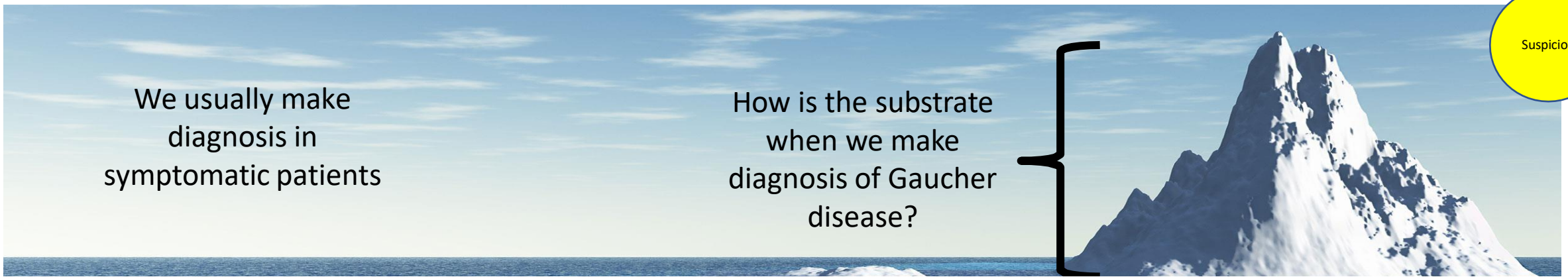
5. Treatment options

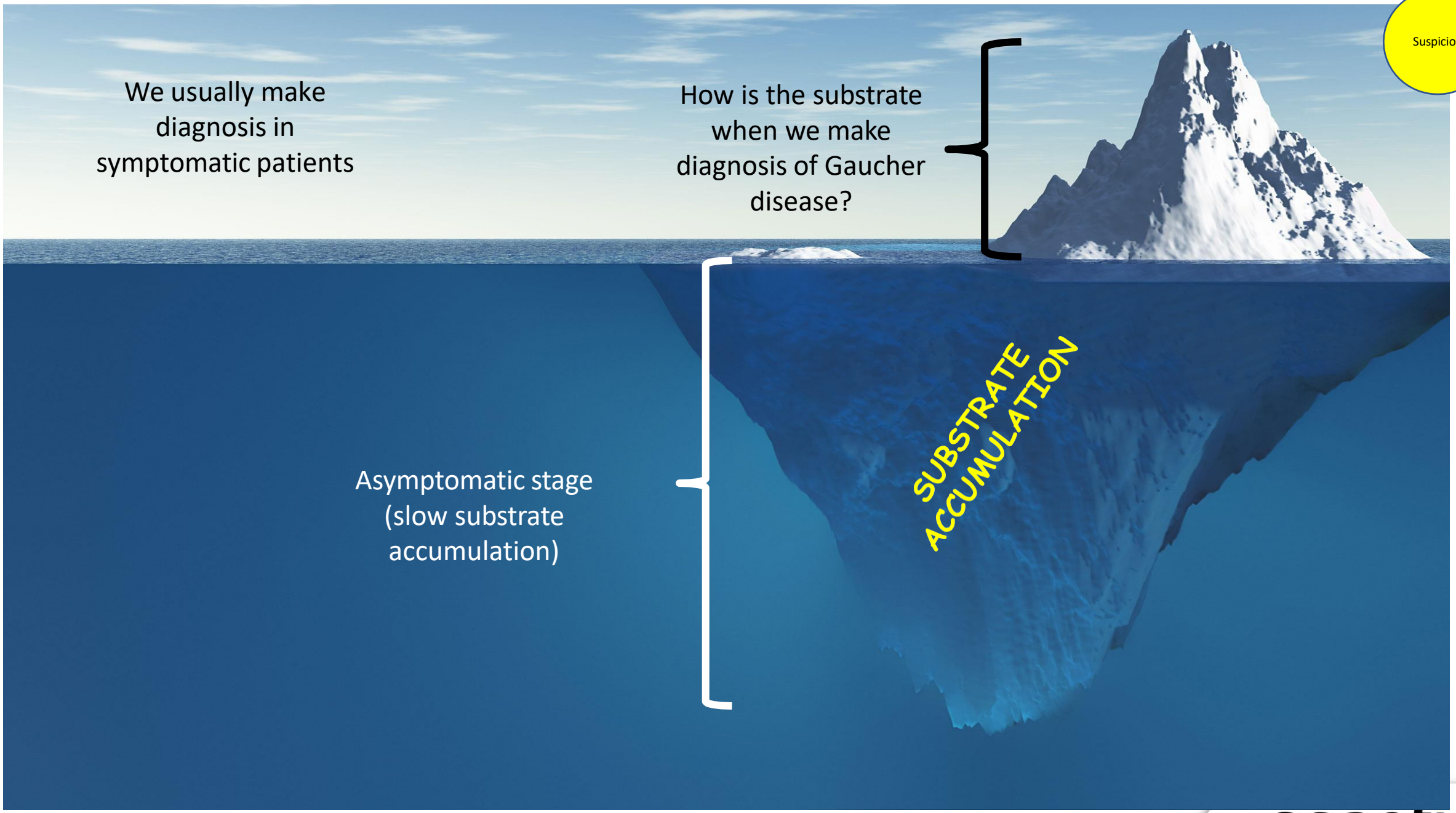
# AGENDA

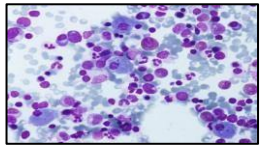
**Therapeutic Opportunities according to therapeutic objectives in Gaucher Disease**

**Therapeutic opportunity = suspicion + diagnosis + baseline**

1. Suspicion + diagnosis


We usually make diagnosis in symptomatic patients
How is the substrate when we make diagnosis of Gaucher disease?
Suspicion


We usually make diagnosis in symptomatic patients
How is the substrate when we make diagnosis of Gaucher disease?
Suspicion
Asymptomatic stage (slow substrate accumulation)
SUBSTRATE ACCUMULATION

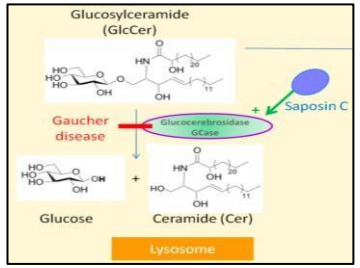

Macrophages

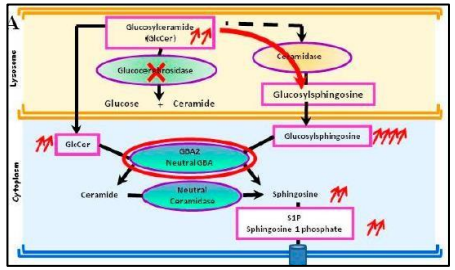
Suspicion

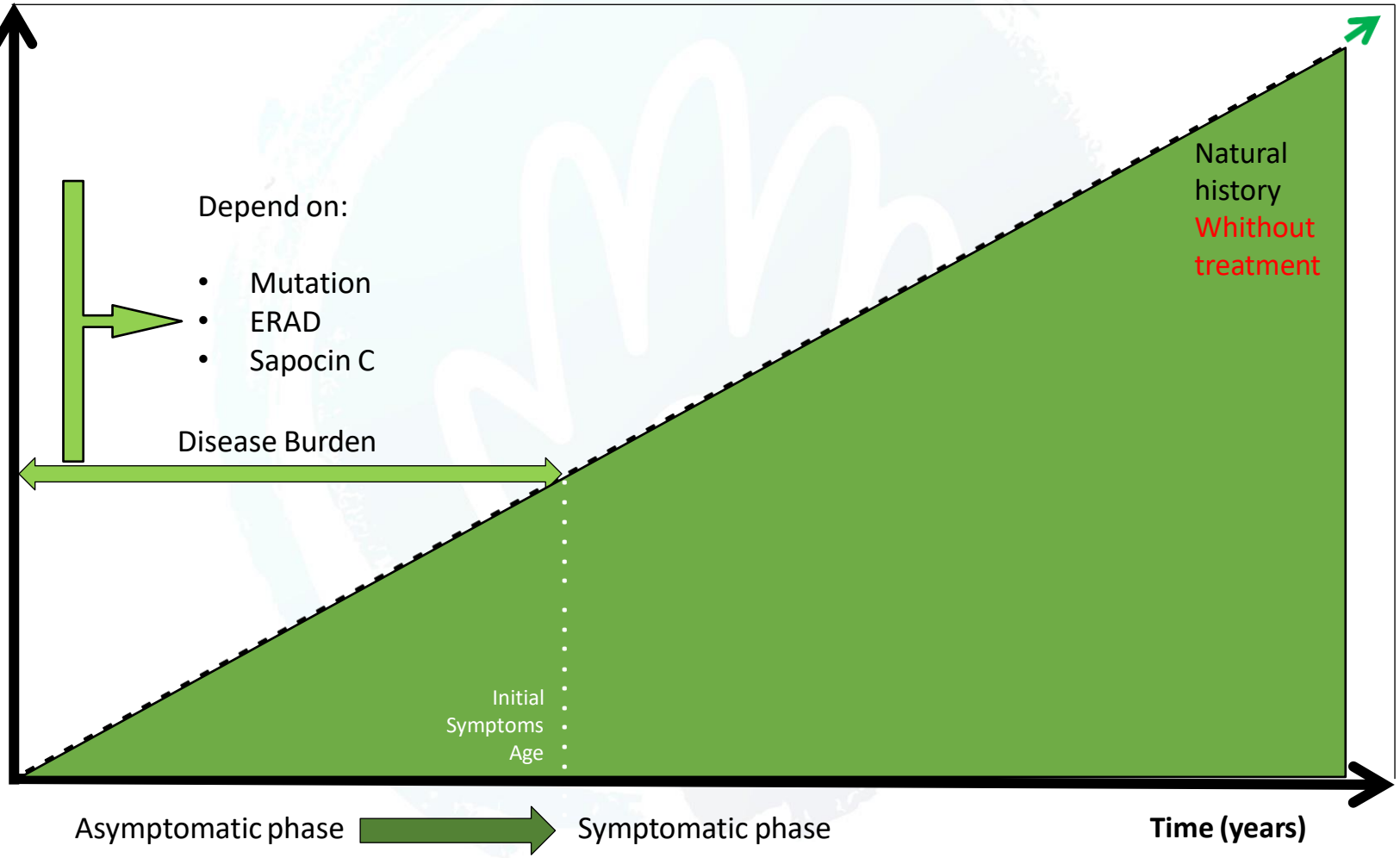
## Gaucher Disease (GD) Type 1 (natural history whithout treatment)

**Substrate Accumulation:**

Glucosylceramide (GL1)
Glucosylsphingosine (lyso – GL1)




example: 8.3 years

**Common manifestations of GD include**:

1. Anemia
2. Thrombocytopenia
3. Splenomegaly
4. Hepatomegaly
5. Bone pain
6. Bone crisis
7. Osteonecrosis
8. Pulmonary Hipertension
9. Splenectomy
10. Pathologic fractures
11. Multiple Mieloma
12. Alpha-sinucleophaties

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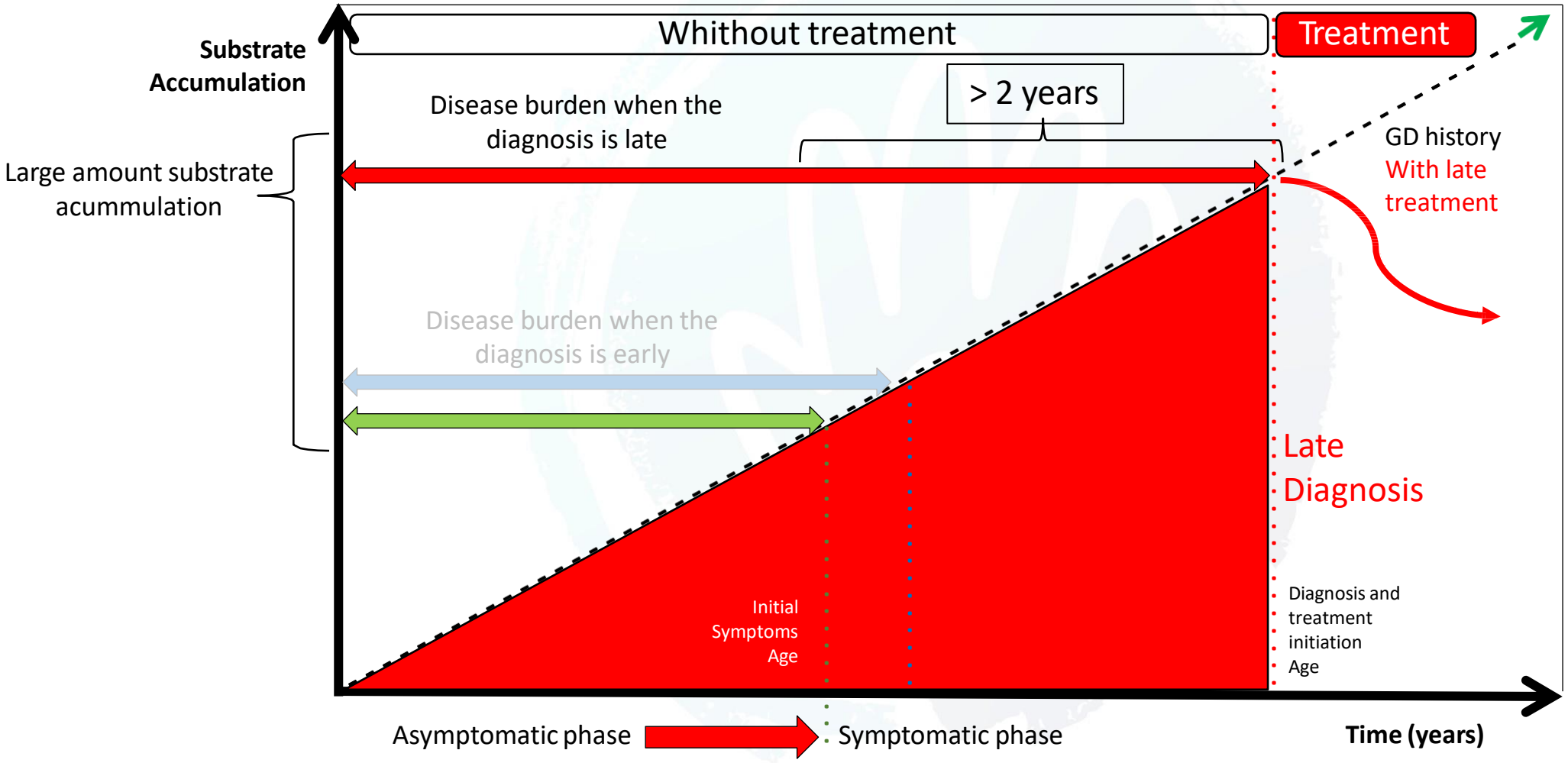
Suspicion

## Fisiopatología de la Enfermedad de Gaucher

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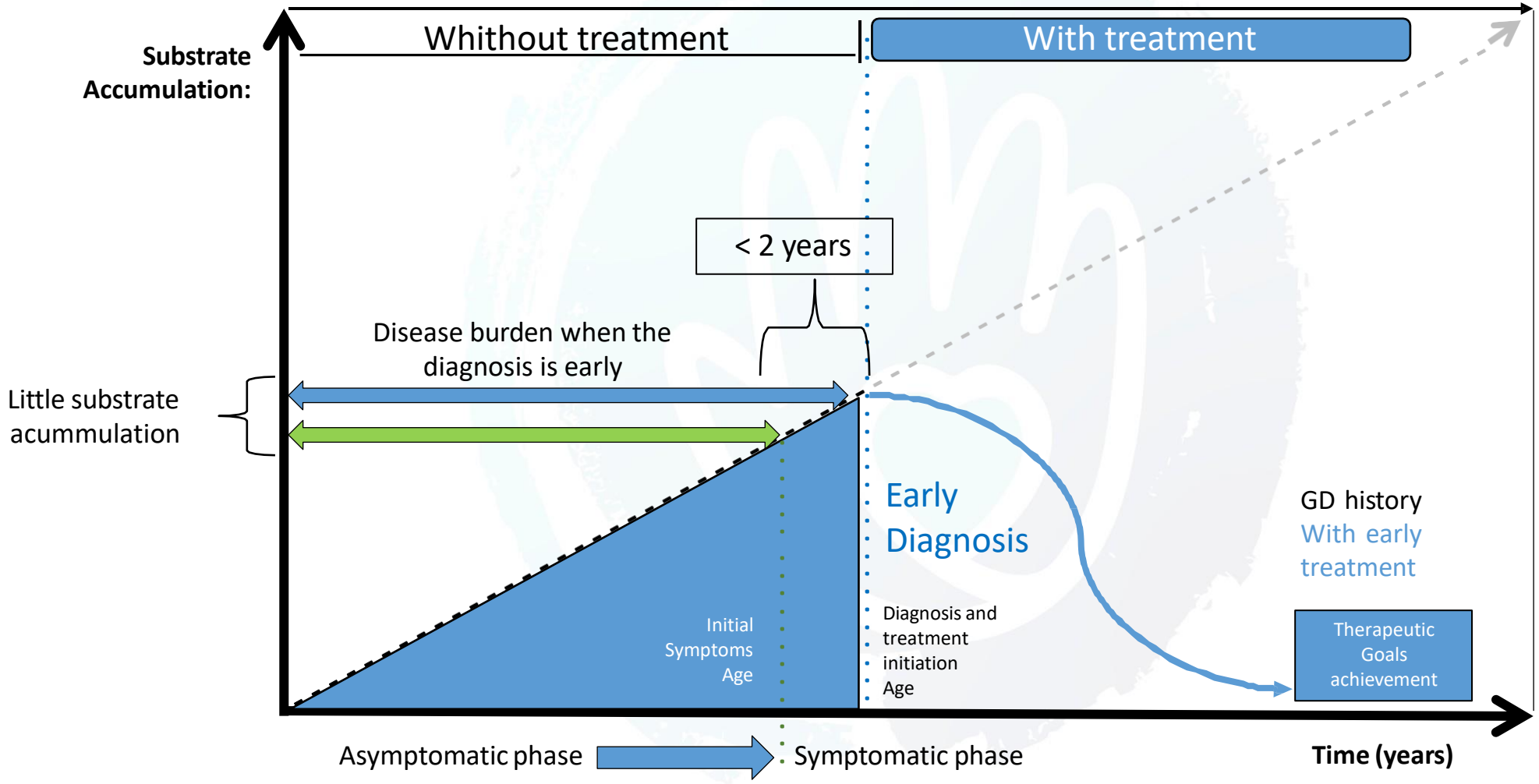
Suspicion

## Gaucher Disease (GD) Type 1

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7. Osteonecrosis
8. Pulmonary Hipertension
9. Splenectomy
10. Pathologpic fractures
11. Multiple Mieloma
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## SUBDIAGNOSIS? YES

Suspicion

## Algorithms? (Experiencia Capellini en Agentina)

Suspicion

### Proyecto Cappellini:

(2015 al 2020)

A. Criterios de inclusión:

1. Esplenomegalia
2. Trombocitopenia (<150.000)

B. Criterios de Exclusión:

1. Enfermedad oncohematológica
2. Anemia hemolítica
3. Hemoglobinopatía

### Proyecto Argentino:

(2018 al 2020)

A. Criterios de inclusión:

1. Trombocitopenia + Anemia o
2. Trombocitopenia + Leucopenia o
3. MGUS / Gamapatía

B. Criterios de exclusión:

1. Pacientes con tratamiento oncológico
2. Pacientes con anemia aplásica severa

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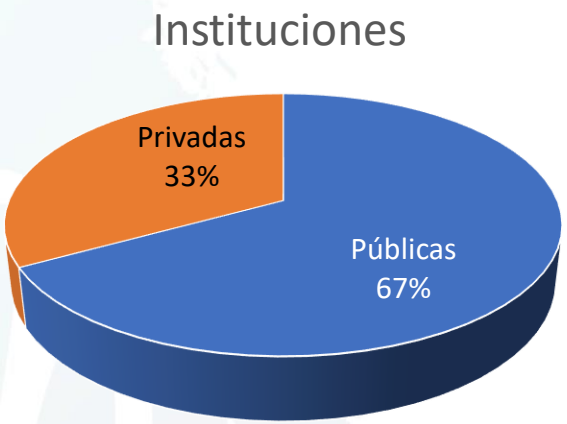
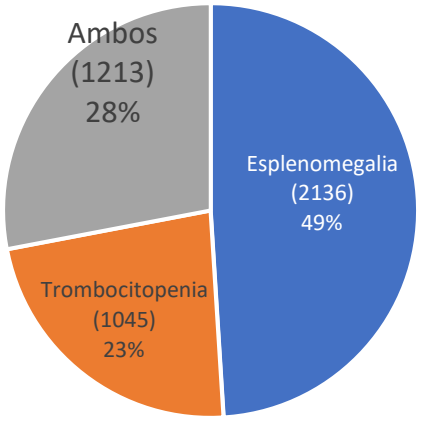
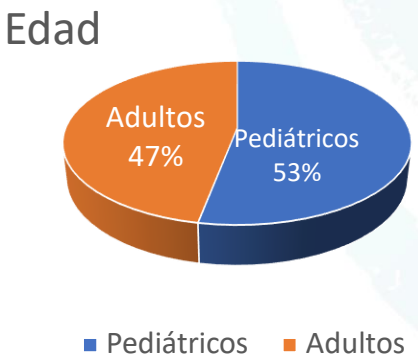
# Algorithms? (Experiencia Capellini en Agentina)

Suspicion


Criterios de inclusión



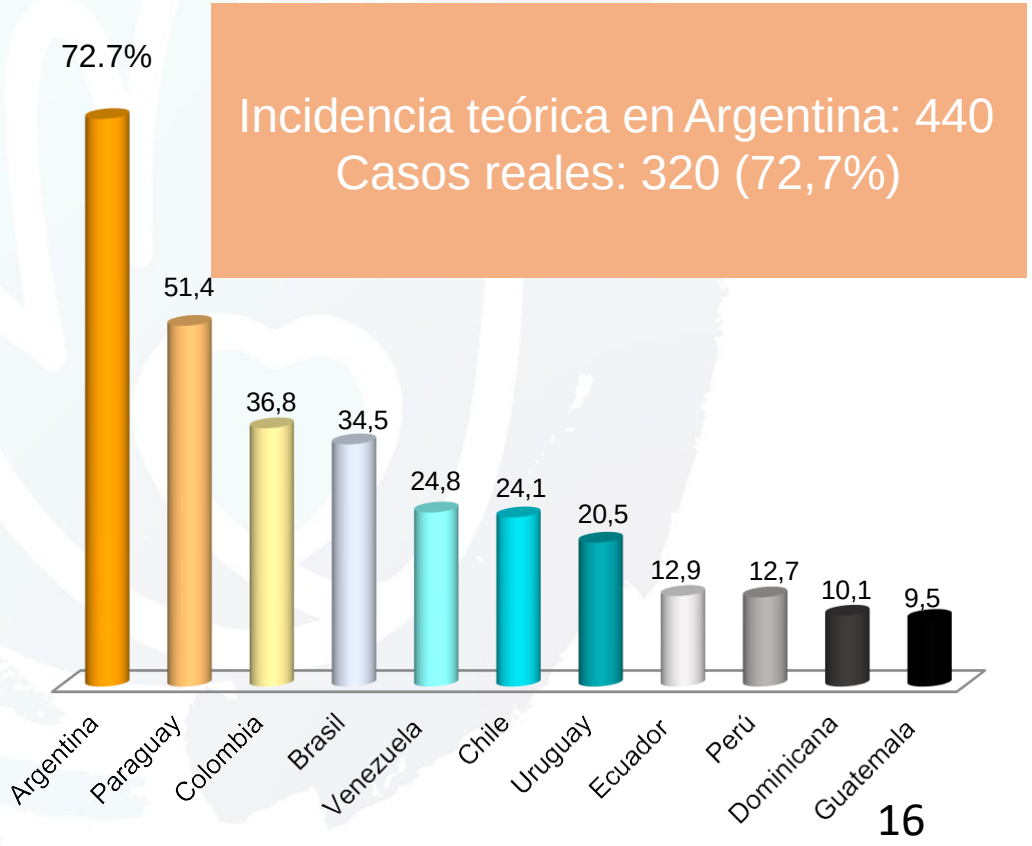

- De un total de 4394 muestras procesadas en 64 meses se diagnosticaron 26 pacientes con EG.

## Algorithms? (Experiencia Capellini en Agentina)

Suspicion

# Tasa de efectividad de Argentina 0.6% vs Italia 3.2%

| Country | Population | Expected Cases | Diagnosed cases |
|---|---|---|---|
| Argentina | 44.406.000 | 440 | 320 (72.7%) |
| Colombia | 50.328.000 | 500 | 184 (36.8%) |
| Brasil | 216.221.000 | 2160 | 746 (34.5%) |
| CHILE | 18.794.000 | 187 | 45 (24%) |
| México | 134.764.000 | 1370 | 101 (7.4%) |
| Perú | 33.213.000 | 330 | 42 (12.7%) |
| Panamá | 4.216.000 | 420 | 1 (0.2%) |
| honduras | 8.602.000 | 86 | 1 (1.1%) |
| El Salvador | 6.203.000 | 62 | 4 (6.4%) |
| Guatemala | 17.865.000 | 178 | 17 (9.5%) |
| Rep. Dominicana | 11.106.000 | 110 | 11 (10%) |
| Costa Rica | 5.047.000 | 50 | 1 (2%) |
| Ecuador | 17.265.000 | 170 | 22 (12.9%) |
| Uruguay | 3.481.000 | 34 | 7 (20.5%) |
| Paraguay | 7.033.000 | 70 | 36 (51.4%) |
| Bolivia | 11.471.000 | 110 | 3 (1.8%) |
| Venezuela | 33.055.000 | 330 | 82 (24.8%) |




Incidencia teórica en Argentina: 440
Casos reales: 320 (72,7%)

## Algorithms? (Experiencia Capellini en Agentina = Proyecto Bioquímico)

Suspicion

Educación médica

Algoritmos diagnósticos simplificados

Nuevos diagnósticos en instituciones sin diagnósticos previos. Aumento de la sospecha diagnóstica en la comunidad médica.

Disminución del retraso en el inicio de la terapia.

2016
X retraso 8 años

2022
X retraso 4,2 años


WHERE'S WALDO?

# Algorithms + Education (PREDIGA experience)

Suspicion

HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

## PB2361 PREDIGA, EDUCATIONAL AND DIAGNOSIS PROJECT IN ACID SPHINGOMYELINASE DEFICIENCY DISEASE (ASMD) AND GAUCHER DISEASE (GD): RESULTS TO THE OBJECTIVE ACHIEVED OF 200 PATIENTS ANALYZED.

Jesus Villarrubia[1], Enrique Calderon[2], Marta Morado[3], Victor Quintero[4], Isidro Vitoria[5], Miguel Angel Torralba[6]

**Aims:**

The main objective of this study is to identify patients with idiopathic splenomegaly or splenectomy as well as to promote awareness and knowledge of ASMD and GD and their diagnosis algorithm through a national medical education program . Prevalence of ASMD and GD in patients with idiopathic splenomegaly or splenectomy will be also established.

Promote awareness, knowledge and diagnosis os ASMF and GD

**Methods:**

Regarding educational program, the participating centers lead clinical sessions as part of the PREDIGA education program. It was planned to impart about 100 clinical sessions within the medical education program and reach 200 patients fulfilling diagnostic criteria for ASMD and GD in the recruitment process.

100 educational clinical sessions
200 patients fulfilling criteria

**Results:**

A total of 206 patients' blood samples have been collected to perform a DBS. Results to date have revealed the diagnosis of 2 ASMD and 4 GD patients derived from the epidemiological program. Thanks to implementation of this educational program 2 ASMD and 1 GD patients were diagnosed. Therefore, in this study the prevalence of ASMD and GD in patients with idiopathic splenomegaly or splenectomy is 0.97% and 1.9% respectively.

2 ASMD patients (0.97%)
4 GD patients (1.9%)

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# Gaucher Diagnostic Testing Scheme in Argentina

Suspicion

Laboratorio Chamoles
Errores Congénitos del Metabolismo

ELSEVIER

Clinica Chimica Acta 317 (2002) 191–197

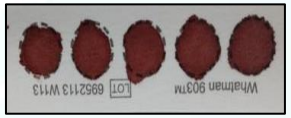
www.elsevier.com/locate/clinchim

Gaucher and Niemann–Pick diseases—enzymatic diagnosis in dried blood spots on filter paper: retrospective diagnoses in newborn-screening cards

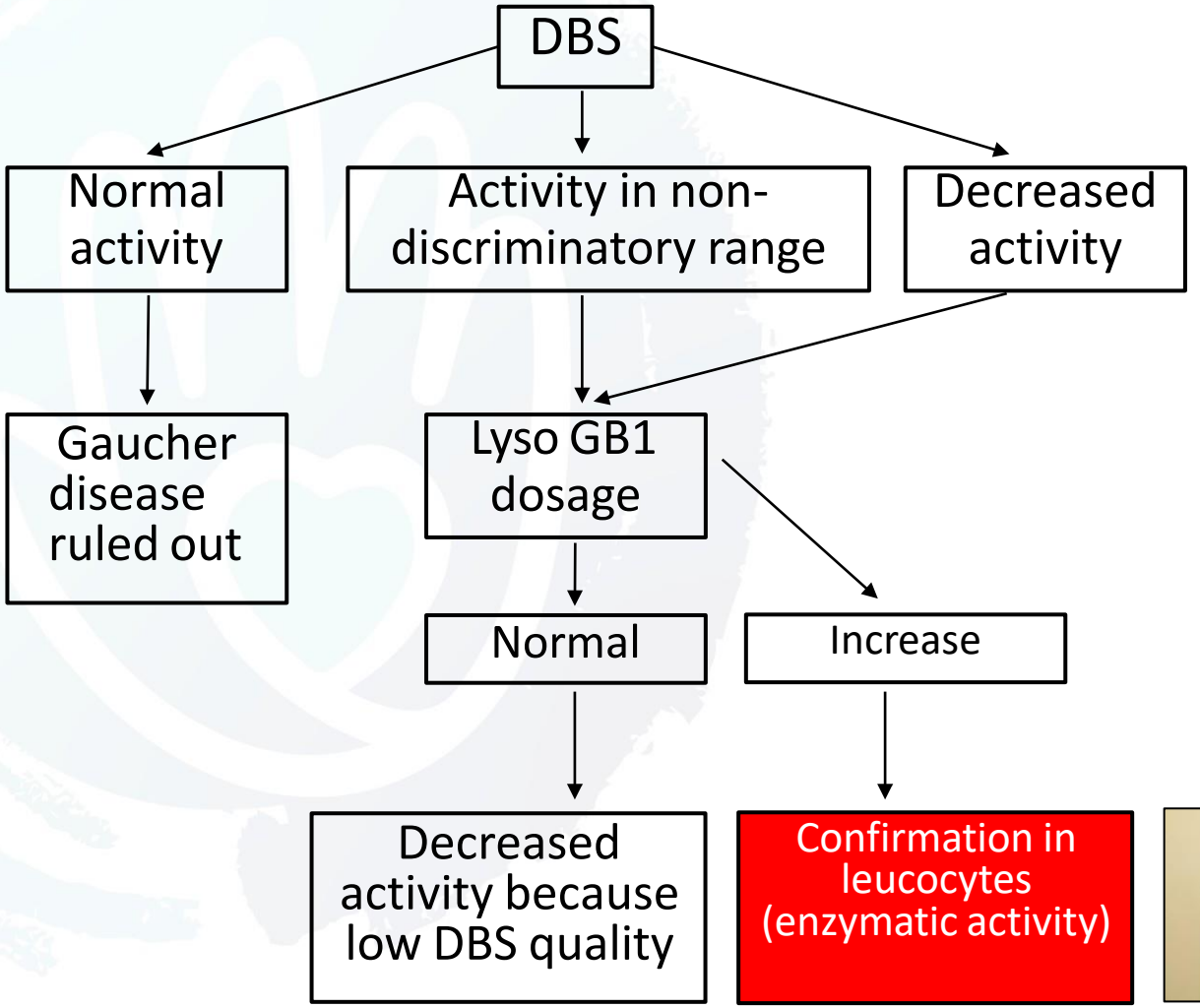
Néstor A. Chamoles *, Mariana Blanco, Daniela Gaggioli, Carina Casentini

*Laboratory of Neurochemistry, Uriarte 2383, 1425 Buenos Aires, Argentina*

Received 2 October 2001; received in revised form 20 November 2001; accepted 20 November 2001




**DBS + Biomarcadores**

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Diagnosis

# Who to treat?

To those patients with a **definitive diagnosis of GD**





## Confirming diagnosis

### Enzyme assay

The diagnostic test for Gaucher disease is the demonstration of low acid β-glucosidase activity in peripheral blood leukocytes (normal range 2.1–5.3 μmol/l/h) [39]. The assay is performed in blood leucocytes using a fluorescent substrate, 4-methyumbelliferone β-glucoside. The test requires 10 cc EDTA blood sample shipped at ambient temperature by overnight delivery to the lab.

### Molecular diagnosis

Molecular analysis of GBA1 gene is complicated by presence of highly homologous pseudogene that harbors several mutations, which if present in the active gene leads to Gaucher disease. A number of techniques have been developed to circumvent potential problems arising from this situation in order to analyze only the active gene sequences uncontaminated by pseudogene sequences [40]. A negative screen for common GBA1 mutations does not exclude Gaucher disease (see discussion). Therefore, undertaking sequencing of the entire coding region of GBA1 gene is recommended in patients strongly suspected of harboring Gaucher disease when a screen for common mutations is negative [40]. Mutation analysis of the GBA1 gene may provide some prognostic information although there is considerable variation of disease severity among patients harboring an identical GBA1 genotype [7] ([Figure 2]). Knowledge of the GBA1 mutation in a proband also facilitates family screening for genetic counseling purposes since heterozygote carriers cannot be reliably identified by enzyme assays.

Consensus Conference: A reappraisal of Gaucher disease - diagnosis and disease management algorithms. Pramod K. Mistry, Maria Domenica Cappellini, Elena Lukina, Hayri Özsan, Sara Mach Pascual, Hanna Rosenbaum, Maria Helena Solano, Zachary Spigelman, Jesús Villarrubia, Nora Watman, and Gero Massenkeil. Am J Hematol. 2011 January ; 86(1): 110–115. doi:10.1002/ajh.21888.

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## Who to treat?

To those patients with a **definitive diagnosis of GD.**

**Consenso para la Enfermedad de Gaucher:**
**Grupo Argentino de diagnóstico y tratamiento de la Enfermedad de Gaucher**

Guillermo Drelichman [1]; Nora Basack[1]; Dr. Nicolás Fernández Escobar [1] Nora Watman [2]; Dra. Moira Bolesina[2]; Graciela Elena [3]; Dr. Samuel Ernesto Veber[3]; Dra. Regina Kohan[4]; Dra. Marta Dragosky [5]; Dra. Isabel Annetta[5]; Dra. Aurora Feliu [6]; Dra. Gabriela Sciuccati[6]; Dra. Maria Fernanda Cuello [7]; Dra. Alcira Fynn [7]; Dra. Raquel Dodelson de Kremer[8]; Dra. Celia J. Angaroni[8]; Dra. Alicia N Giner-Ayala[8]; Dra. Ana Oller de Ramirez[8]; Dr. Norberto B. Guelbert[8]; Dra. María Andrea Delgado[8]; Dra. Adriana Becerra[8]; Dra. Beatriz Oliveri [9]; Dra. María Silvia Larroudé [10]; Dra. Francisca María Masllorens [11]; Dra. Marina Szlago[12]; Dra. Andrea B. Schenone[12]; Aguilar G[13]; Volpacchio M[13].

ARTICULO ORIGINAL

Diagnosis

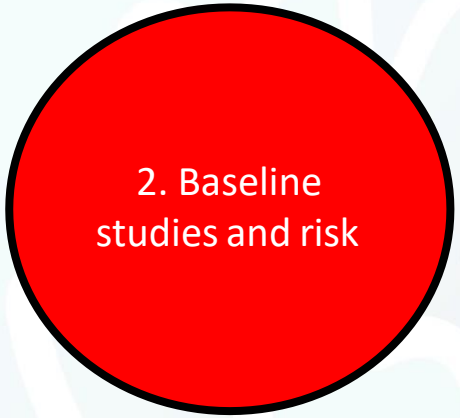
**Tabla 2:** Diagnóstico de la EG:

| DIAGNÓSTICO | VENTAJAS | DESVENTAJAS |
|---|---|---|
| ENZIMÁTICO | ♦ Los leucocitos de sangre periférica o el cultivo de fibroblastos [16] son el material de elección para el estudio enzimático,<br>♦ Desde el año 2002, como fruto de un desarrollo científico argentino, se cuenta con las gotas de sangre en papel de filtro [18] permitiendo la identificación de pacientes y posibilitando el envío de muestras a distancia, el diagnóstico retrospectivo y el eventual tamizaje poblacional. [19] | ♦ No predice la severidad clínica de la enfermedad.[17]<br>♦ Con un resultado anormal en gotas de sangre: recurrir a la confirmación en leucocitos.<br>♦ En heterocigotos puede superponerse con el de la población normal impidiendo el uso del ensayo enzimático para la detección de heterocigotos [20, 21,22] |

# AGENDA

**Therapeutic Opportunities according to therapeutic objectives in Gaucher Disease**

**Therapeutic opportunity =**



# Baseline studies



**Table 2** Initial Assessment

- A complete history of patient and family, preferably including a pedigree
- A comprehensive physical examination (annual)
- Quality of life (annual): Patient-reported functional health and well-being (SF-36 Health Survey)
- Blood tests
  - Primary tests
    - Hemoglobin
    - Platelet count
  - Biochemical markers (one or more of these biochemical markers should be consistently monitored in conjunction with other clinical assessments of disease activity; chitotriosidase, when available as a validated procedure, may be the most sensitive indicator of changing disease activity, and is therefore preferred)
    - Chitotriosidase
    - ACE
    - TRAP
  - Additional blood tests (to be evaluated selectively based on each patient's age and clinical status)
    - WBC, PT, and PTT;
    - Iron, iron binding capacity, ferritin, vitamin $B_{12}$;
    - AST and/or ALT; alkaline phosphatase; calcium, phosphorous, albumin, total protein, total and direct bilirubin;
    - Serum immunoelectrophoresis
    - Hepatitis profile
- β-glucosidase and mutation analysis
- Antibody sample*
- Visceral (contiguous transaxial 10-mm thick sections for sum of region of interest)
  - Spleen volume (volumetric MRI or CT)
  - Liver volume (volumetric MRI or CT)
- Skeletal
  - MRI (coronal; T1- and T2-weighted) of the entire femora
  - X-ray (AP view of the entire femora)† and lateral view of the spine
  - DXA lumbar spine and femoral neck
- Pulmonary (recommended every 12-24 months for patients with borderline or above normal pulmonary pressures at baseline)
  - ECG, chest x-ray, and
  - Doppler echocardiogram (right ventricular systolic pressure) for patients >18 years old

Abbreviations: ACE, angiotensin-converting enzyme; TRAP, tartrate-resistant acid phosphatase; AP, anterior-posterior; ALT, alanine transaminase; AST, aspartate transaminase; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; MRI, magnetic resonance imaging; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cells.

*A baseline sample to be stored at Genzyme Corporation; an optional subsequent sample at 6 months after starting enzyme replacement therapy (ERT). The samples will be tested only if clinically indicated such as for a suspected immune-mediated adverse event, or for suspected loss of ERT effectiveness.

†Optimally from hips to below knees.

Physical examination

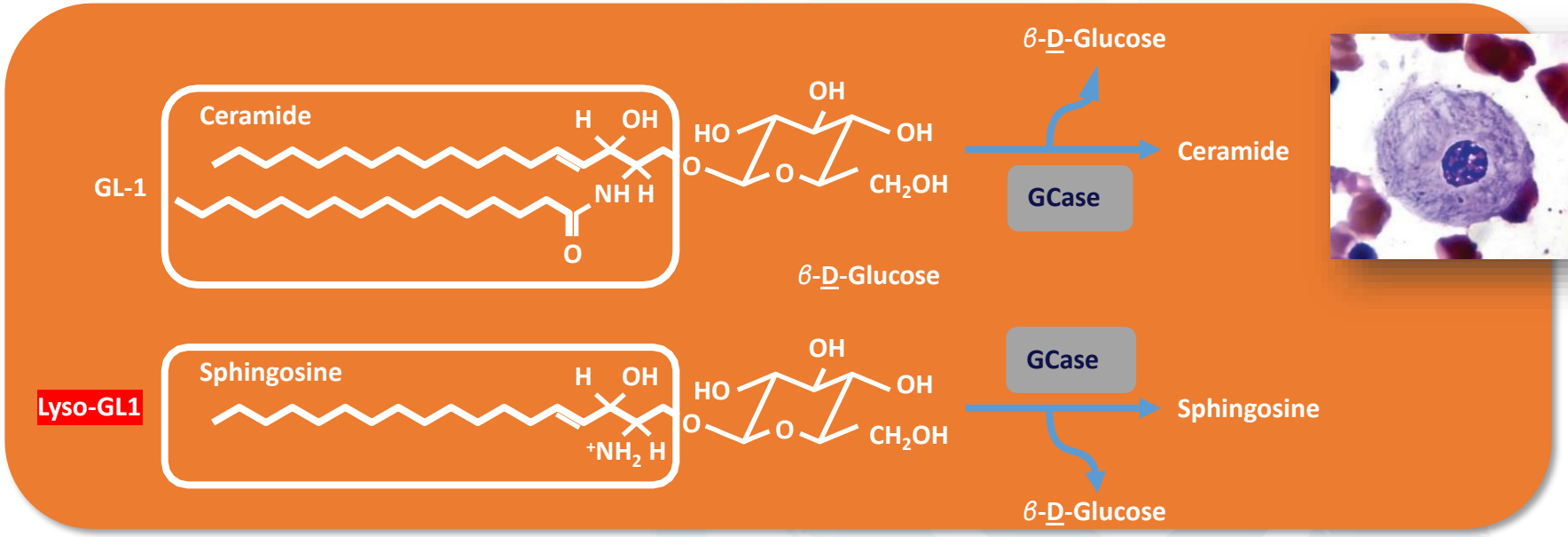
Blood tests

- CBC
- Hb
- Platelet count

Images

Gaucher Disease Type 1: Revised Recommendations on Evaluations and Monitoring for Adult Patients
Neal J. Weinreb,a Mario C. Aggio,b Hans C. Andersson,c Generoso Andria,d Joel Charrow,e Joe T.R. Clarke,f Anders Erikson,g Pilar Giraldo,h Jack Goldblatt,i Carla Hollak,j Hiroyuki Ida,k Paige Kaplan,l Edwin H. Kolodny,m Pramod Mistry,n Gregory M. Pastores,m Ricardo Pires,o Ainu Prakesh-Cheng,p Barry E. Rosenbloom,q C. Ronald Scott,r Elisa Sobreira,s, Anna Tylki-Szyman´ ska,t Ashok Vellodi,u Stephan vom Dahl,v Rebecca S. Wappner,w and Ari Zimranx. Seminhematol.2004.07.010

# Glucosylceramide (GL-1) is the Primary Accumulating Lipid in GD






- GL-1 is a component of cell membranes and precursor of complex glycosphingolipids found in receptors and lipid rafts.
- **Lyso-GL1** accumulates via activation of an alternative metabolic pathway, ceramidase—it is a toxic bioactive lipid.

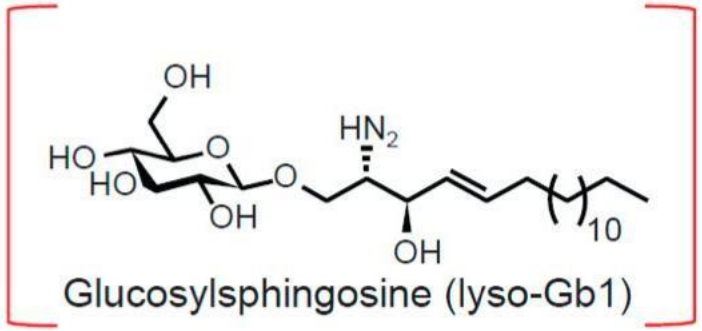

Mielke MM, et al. *PLoS One*. 2013;8:e73094; Dekker N, et al. *Blood*. 2011;118:e118-27;
Grabowski GA, et al. In: Beaudet A, et al (eds). *The Online Metabolic and Molecular Basis of Inherited Metabolic Disease*. 2010.

# Biomarkers in GD



The properties of an ideal biomarker in GD should meet the following criteria:

- Easily measurable and stable in easily accessible sample.
- Be specific and sensitive for GD.
- Accurately reflect the presence and activity of GD
- Predict significant clinical changes
- Have a direct role in the pathophysiology of GD
- Absence of genetic variation
- Change in a tangible and measurable way with treatment
- Be applicable to all patients
- Have an affordable cost to make it feasible



Glucosylsphingosine (lyso-Gb1)

Lyso-GL1 correlation

Correlation with established biomarkers
Fall dramatically with imiglucerase ERT
Monitoring patients on or off therapy
Extent of disease burden and residual disease
Correlate with liver volume and spleen volume, platelet counts and age
Role in immune dysregulation
Skeletal disease
Chronic metabolic inflammation

Baseline studies

# Biomarcadores en EG

Baseline studies

Gaucher Disease

ARTICLE

## Accuracy of chitotriosidase activity and CCL18 concentration in assessing type I Gaucher disease severity. A systematic review with meta-analysis of individual participant data

Tatiana Raskovalova,[1] Patrick B. Deegan,[2] Pramod K. Mistry,[3] Elena Pavlova,[2] Ruby Yang,[3] Ari Zimran,[4] Juliette Berger,[5,6] Céline Bourgne,[5,6] Bruno Pereira,[7] José Labarère[8,9] and Marc G. Berger[5,6,10]

Ferrata Storti Foundation

Haematologica 2021

*Am J Hematol*. 2016 November ; 91(11): 1082–1089. doi:10.1002/ajh.24491.

## Glucosylsphingosine is a key Biomarker of Gaucher Disease

**Vagishwari Murugesan**[1], **Wei-Lien Chuang**[2], **Jun Liu**[1], **Andrew Lischuk**[3], **Katherine Kacena**[4], **Haiqun Lin**[5], **Gregory M Pastores**[6], **Ruhua Yang**[1], **Joan Keutzer**[2], **Kate Zhang**[2], and **Pramod K Mistry**[7]

International Journal of *Molecular Sciences*

MDPI

*Article*

## Treatment Efficiency in Gaucher Patients Can Reliably Be Monitored by Quantification of Lyso-Gb1 Concentrations in Dried Blood Spots

Claudia Cozma [1,†], Paskal Cullufi [2,†], Guido Kramp [1], Marina Hovakimyan [1], Virtut Velmishi [2], Agim Gjikopulli [2], Sonila Tomori [2], Steffen Fischer [1], Sebastian Oppermann [1], Ulrike Grittner [1,3,4], Peter Bauer [1], Christian Beetz [1,*] and Arndt Rolfs [1]

International Journal of *Molecular Sciences*

MDPI

*Review*

## Value of Glucosylsphingosine (Lyso-Gb1) as a Biomarker in Gaucher Disease: A Systematic Literature Review

Shoshana Revel-Vilk [1,2], Maria Fuller [3,4,*] and Ari Zimran [1,2]

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## Baseline studies: Biomarkers

Baseline studies

| Desired characteristics | Chitotriosidase | CCL-18 | GL - 1 | Lyso GL -1 |
|---|---|---|---|---|
| Elevated in GD | Yes | Yes | No | Yes |
| No overlap with normal values | Yes | Yes | No | Yes |
| Decreases with treatment | Yes | Yes | Yes | Yes |
| Highly specific of GD | No | No | Yes | Yes |
| Measure in all patients with GD | No | Yes | Yes | Yes |
| Measure in plasma and DBS | Yes | Yes | Yes | Yes |
| Does not require knowledge about the genotype | No | Yes | Yes | Yes |
| Related to the pathophysiology of GD | No | No | Yes | Yes |

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# Prognostic Biomarkers of Bone Disease

***Proyecto de Colaboración entre Yale y Grupo Argentino de Diagnóstico y Tratamiento de la EG (GADTEG)***

**Investigadores principales: Dr. G. Drelichman[1]; Dra. A. Schenone[2]; Dr. P.K. Mistry[3].**
**Coordinación de los estudios en la Universidad de Yale, New Haven. USA: Dr. Dr. P.K. Mistry[3]**
**Coordinación de los estudios en Argentina: Dr. N. Fernández Escobar[1]**
**[1] Hospital R. Gutiérrez; [2] Laboratorio Dr. N.A. Chamoles; [3] ; Universidad de Yale, New Haven. USA**

Sub-investigadores: Grupo Argentino para el Diagnóstico y Tratamiento de la Enfermedad de Gaucher: Aguilar G, Álvarez Bollea A, Arizo A, Aznar M, Bacciedoni V, Baduel C, Barazzutti L, Barbieri M, Bietti J, Bolesina M, Borchichi S, Braxs C, Brun M, Buchovsky G, Cabral Castella A, Calvo M, Cannigia M, Cranco S, Carvani A, Carro G, Cedola A, Cejas B, Chain J, Colimodio R, Corrales M, Cuello F, Dagostino D, De Ambrosio P, Del Rio F, Damiani G, Dra. Detoni D ,Do Santos S, Dragosky M, Degano A, Diez B, Donato H, Elena G, Esquivel N, Feliu A, Fernandez G, Franco L, Fynn A, Galvan G, Girardi B, Gomez S, Guelbert N, Kantor G, Larroude M, Marino A , Maro A Marquez M, Medicci H, Meschengieser S, Muller K, Mur N, Nakaschian P, Nisnovich G, Núñez G, Nucifora E, Pujal G, Pujol M, Papucci M, Pusseto L, Quijano S, Rapetti M, Reichel P, Richard L, Jaureguiberry R, Rocaspana A, Rossi N. G, Rubulotta E, Saavedra J, Saieg M, Salvador T, Sanabria A, Schwery M, Simon H, Soberon B, Tosin F, Veron D, Watman N, Welsh V, Zarate G, Zirone S

# Análisis de Biomarcadores en EG (Yale –

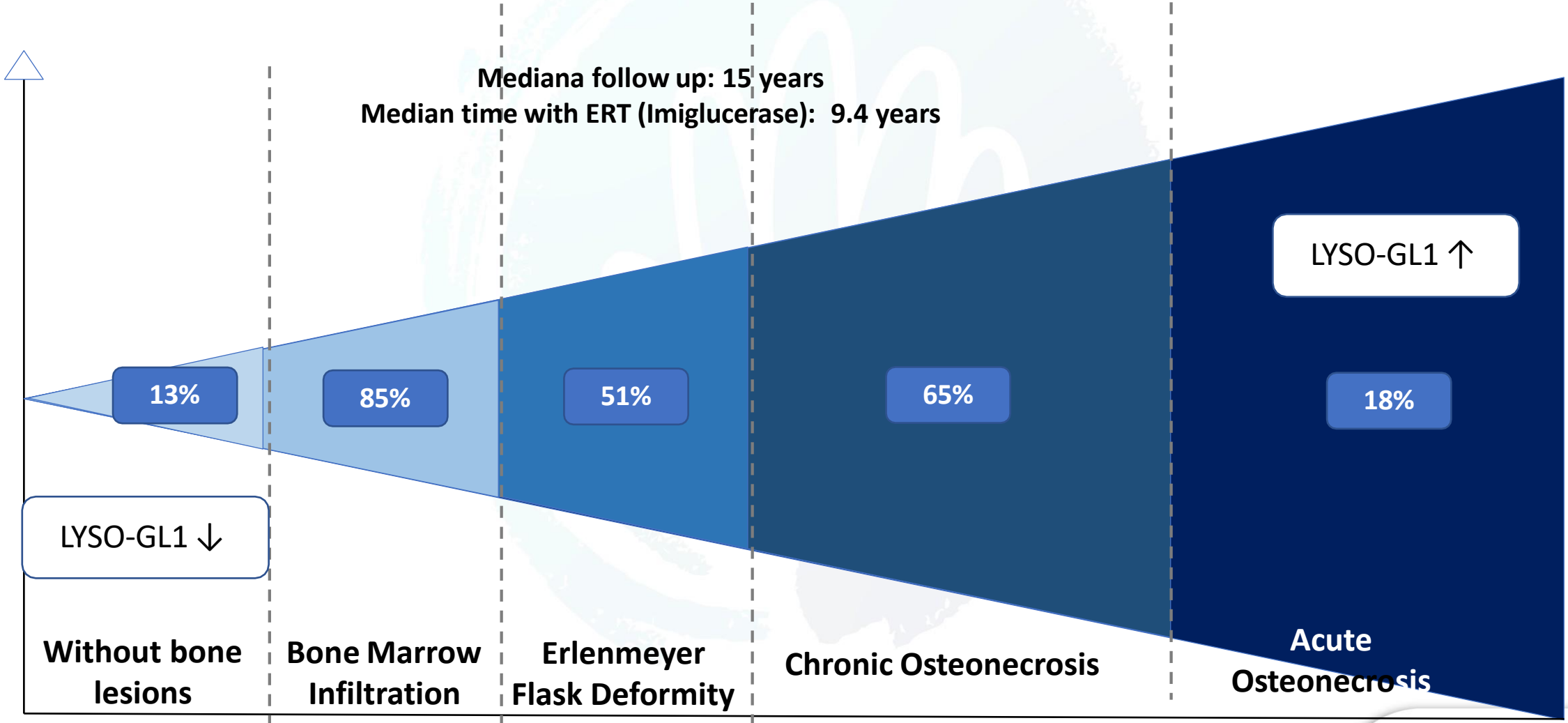
| Test de Kruskal Wallis | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **CCL-18** | **C5a** | **GPNMB** | **Chito** | **MIP-1ß** | **Lyso-GL1** | **IL-1b** | **IL-6** | **TNFα** |
| Chi-squared | 1,334 | 9,285 | 5,448 | 13,270 | 6,657 | **24,600** | 2,142 | 1,348 | 5,800 |
| P-value | ,856 | ,054 | ,244 | **,010*** | ,155 | **< ,001*** | ,710 | ,853 | ,215 |

***Univariable analysis***

****Two biomarkers correlated significantly with progression of bone disease***

***Higher values > higher bone compromise***

# Bone stages: GADTEG data – BONE DISEASE CASCADE




Drelichman G et al. American Journal of Hematology, Vol. 91, No. 10, October 2016

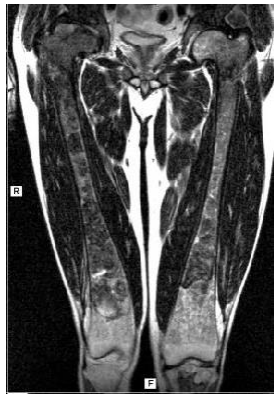
**Baseline studies** - **Images**

# Images in GD

Baseline studies

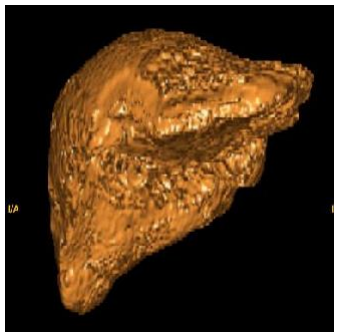
## Identification

### Bone lesions



Ex: BM infiltration

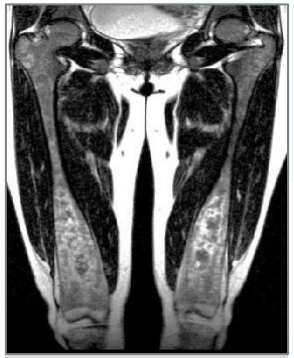
### Hepatomegaly Esplenomegaly



Example: Hepatomegaly

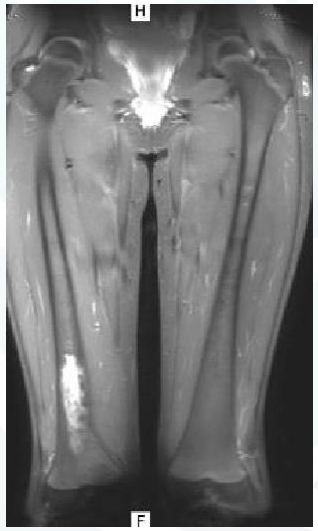
## Caracterization

### Infiltration



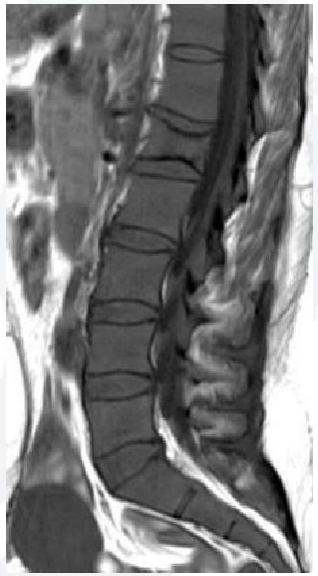
Ex: BM infiltration

### Acute bone lesion



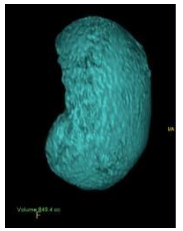
Ex: Bone marrow infarct

### Chronic bone lesion

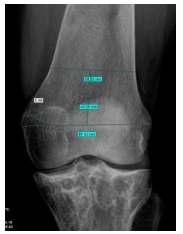


Example: Fracture

## Cuantification

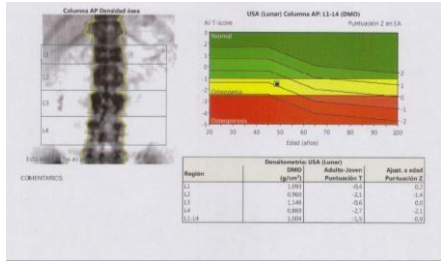


volumes



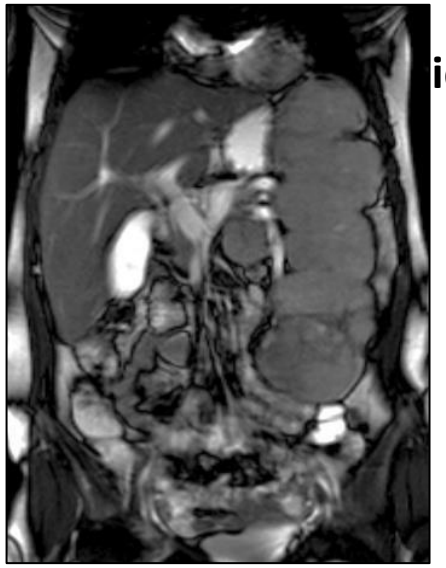
Ex: EFD

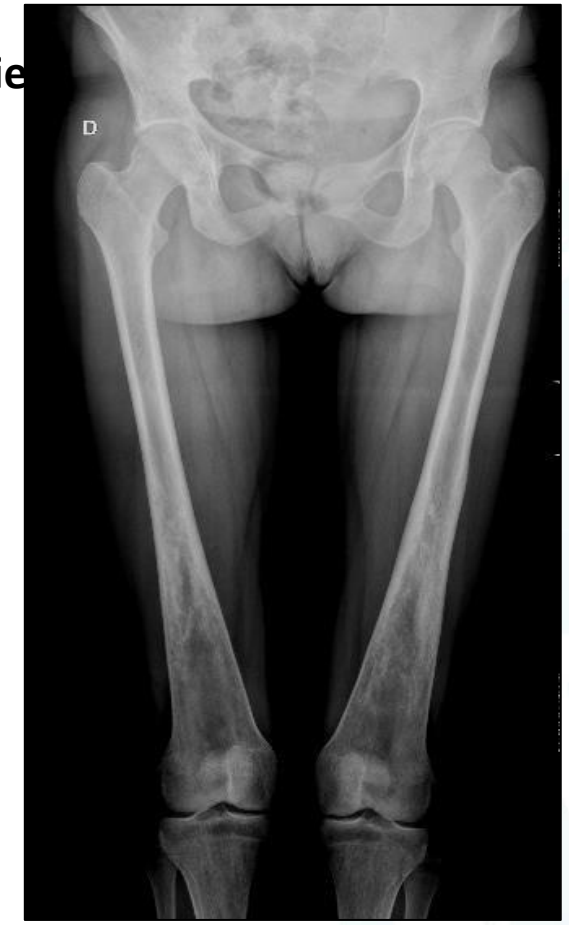
Bone Marrow Burden
Dusseldorf Score
Fat Fraction
Volumetry
Erlenmeyer
Densitometry

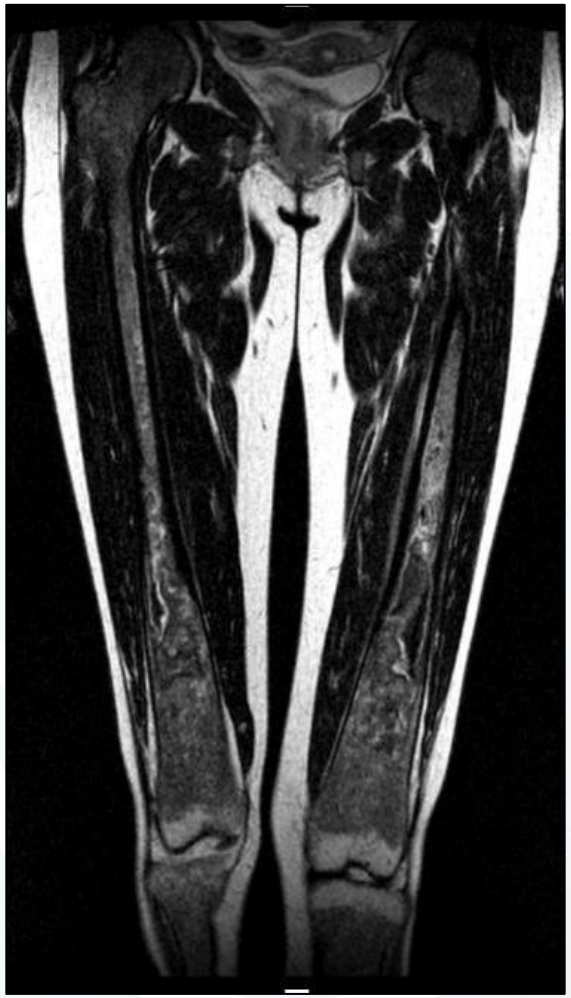


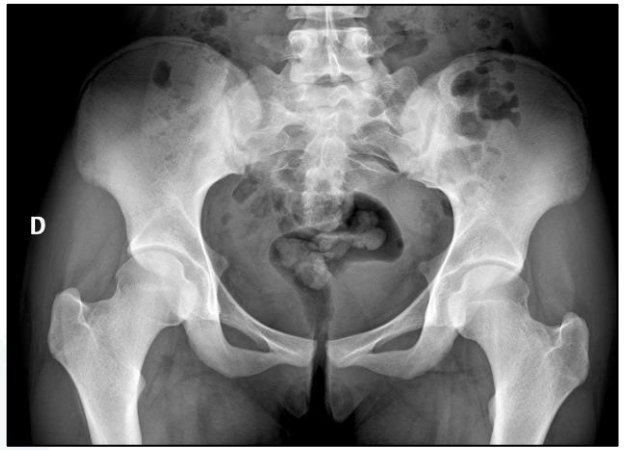
DEXA

ie

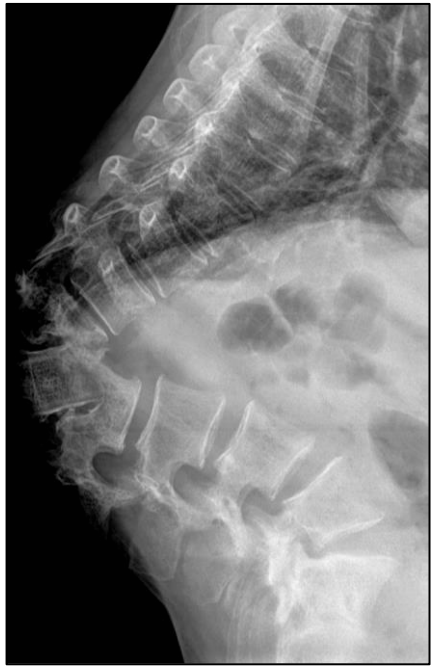


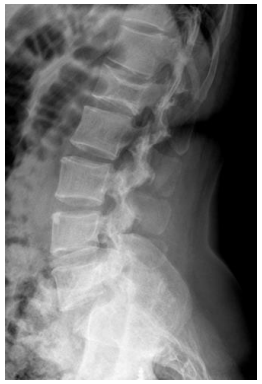


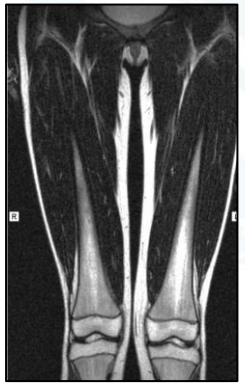





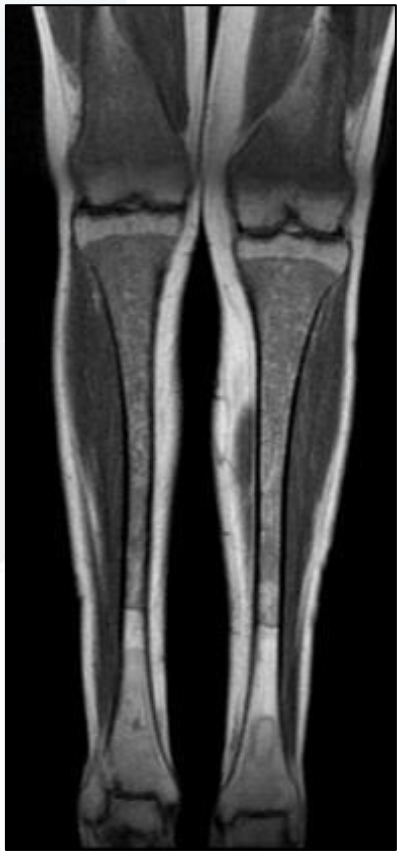

Baseline studies

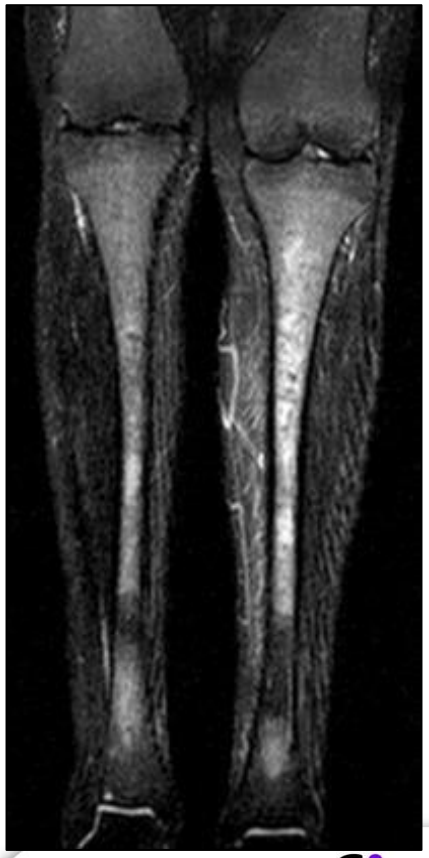






Es crucial conocer el status óseo de los pacientes previo al incio de la TRE o TRS





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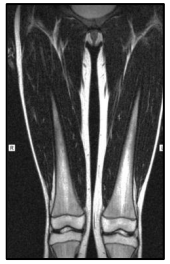
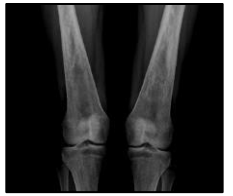
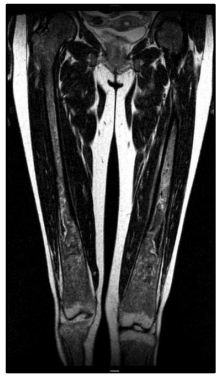
# Metodología para estudiar el compromiso óseo
## Tipos de lesiones



| | Tipo de lesión | Ubicación | Evolución |
|---|---|---|---|
| **LO reversible a la TRE** | Infiltración de la MO con células de Gaucher | MO en general | Hallazgo en la RM: hipointensidad en T1 y T2 e hiperintensidad en STIR. La infiltración responde a la TRE en un plazo de 2 a 3 años |
| | Deformidad de Erlenmeyer | Huesos largos, región diafiso-metafisaria | En la edad pediátrica puede ser reversible con la TRE en un plazo de 3 a 4 años. En adultos es generalmente irreversible |
| **LO irreversible a la TRE (osteonecrosis)** | Infartos óseos | Lesiones metafiso-diafisaria que afectan el hueso medular | Las lesiones por osteonecrosis generalmente se observan en la RM como hipointensas en secuencias SE T1 e hiperintensas en T2 y Stir.<br>Las lesiones óseas irreversibles pueden ser:<br>**1) Crónicas (secuelares)**: en la RM se observa imagen de osteonecrosis sin características de actividad en la secuencia STIR<br>**2) Agudas:** lesiones óseas nuevas que en la secuencia STIR presenta signos de actividad o edema (imagen hiperintensa perilesional) |
| | Necrosis | Afectación epifisaria que involucra hueso cortical y subcondral, pudiendo debilitarlo llevándolo al colapso y alteración de la articulación. | |







*Grupo Argentino de Diagnóstico y Tratamiento de la EG*

# Baseline studies – Risk stratification

Risk





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# When to start treatments? Risk stratification

Risk

**Table 1**
Children (< 18 years) with Gaucher disease: Risk assessment

| Increased Risk | All Others |
|---|---|
| One or more of the following in addition to physical signs: | All children with any relevant physical signs or manifestations of Gaucher disease should be treated with ERT |
| Symptomatic disease, including manifestations of abdominal or bone pain, fatigue, exertional limitations, weakness, and cachexia | |
| Growth failure | |
| Any evidence of skeletal involvement, including Erlenmeyer flask deformity (EFD) | |
| Platelet count ≤ 60,000 mm$^3$ and/or documented abnormal bleeding episode(s) | |
| Hemoglobin ≤ 2.0 g/dL below lower limit of normal for age and sex | |
| Impaired quality of life (QOL) due to Gaucher disease | |

Fatigue?

Bone marrow infiltration?

**Table 2**
Adults with Gaucher disease: Risk assessment

| Increased risk | Lower risk |
|---|---|
| One or more of the following: | Level of disease meets ALL of the following: |
| Symptomatic skeletal disease | Normal liver, cardiac, lung and renal functions<br>Minimal impairment of QOL<br>No obvious or recent rapid progression of disease manifestations<br>Skeletal disease limited to mild osteopenia and Erlenmeyer flask deformity<br>Hemoglobin > 10.5 g/dL for females and > 11.5 g/dL for males (or not more than 2.0 g/dL below lower limit of normal for age and sex)<br>Platelet count > 60,000 mm$^3$ on three determinations<br>Liver volume < 2.5 × normal<br>Spleen volume < 15 × normal |
| Moderate to severe osteopenia | |
| Chronic bone pain | |
| Bone crises | |
| Avascular necrosis | |
| Pathological fractures | |
| Joint replacement(s) | |
| Impaired QOL due to Gaucher disease | |
| Cardiopulmonary disease, including pulmonary hypertension | |
| Platelet count ≤ 60,000 mm$^3$ or documented abnormal bleeding episodes | |
| Symptomatic anemia or hemoglobin ≤ 8.0 g/dL | |
| Transfusion dependency | |
| Significant liver disease | |
| Hepatomegaly that is 2.5 × normal | |
| Infarcts | |
| Portal hypertension | |
| Hepatitis | |
| Significant splenic disease | |
| Splenomegaly that is ≥ 15 × normal | |
| Infarcts | |
| Significant renal disease | |
| Any concomitant medical condition that further complicates or exacerbates Gaucher disease or its signs and symptoms | |

with:
Mild anemia
Mild thrombocytopenia
Mild splenomegaly
Mild hepatomegaly
What happens with asymptomatic patients with values between the normal range?

Genetics In Medicine. Individualization of long-term enzyme replacement therapy for Gaucher disease. *Hans C. Andersson, Joel Charrow, Paige Kaplan, Pramod Mistry, Gregory M. Pastores, Anna Prakash-Cheng, Barry E. Rosenbloom, C. Ronald Scott, Rebecca S. Wappner, and Neal J. Weinreb, for the International Collaborative Gaucher Group U.S. Regional Coordinators.* February 2005, Vol. 7: No. 2

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# Baseline studies - Risk

Risk

**Tabla 4:** Clasificación de grupos de riesgo para iniciar el tratamiento[57]
*Modificado por el Grupo Argentino de Diagnóstico y Tratamiento de la EG*

| **Riesgo aumentado** (uno o más de los siguientes aspectos) | **Riesgo bajo** (ausencia de signos o de evolución rápida de la EG) |
|---|---|
| • Enfermedad ósea asintomática-sintomática<br>• Síntomas óseos: dolor óseo-crisis ósea | • Calidad de vida mínimamente afectada<br>• Función hepática, cardíaca, pulmonar y renal normal |
| • Osteopenia moderada a severa<br>• Lesiones óseas reversibles (infiltración ósea Erlenmeyer)<br>• Lesiones óseas irreversibles (infartos- necrosis óseas)<br>• Fracturas patológicas-reemplazos articulares | • Sin enfermedad ósea |
| • Anemia sintomática o Hb < 8 g/dl<br>• Dependencia transfusional | • Hb > 10,5 g/dl |
| • Recuento de plaquetas < 60 x $10^9$/l<br>• Episodios de sangrados documentados | • Recuento de plaquetas > 60 x $10^9$/l |
| • Hepatomegalia > 2,5 veces lo normal.<br>• Hepatitis-Hipertensión portal-Infartos hepáticos | • Hígado < 2,5 veces lo normal |
| • Esplenomegalia > 15 veces lo normal<br>• Infartos esplénicos | • Bazo < 15 veces lo normal |
| • Calidad de vida alterada por la EG | • No |
| • Enfermedad cardiopulmonar incluida la hipertensión pulmonar | • No |
| • Enfermedad renal | • No |
| • Cualquier situación que complique o exacerbe a la EG o sus signos o síntomas | • No |

**PED**

**HIGH RISK**
INITIAL DOSE = ERT: 60 U/kg/EOW

**ADULTS**

**HIGH RISK**
INITIAL DOSE = ERT: 60 U/kg/EOW

**LOW RISK**
INITIAL DOSE = ERT: 30 U/kg/EOW

# AGENDA

**Therapeutic Opportunities according to therapeutic objectives in Gaucher Disease**

## Therapeutic opportunity =

3. When to start treatment? Doses

## Starting doses?

How do you decide on a starting dose?

Children

When?

**Table 1**
Children (< 18 years) with Gaucher disease: Risk assessment

| Increased Risk | All Others |
|---|---|
| One or more of the following in addition to physical signs: | All children with any relevant physical signs or manifestations of Gaucher disease should be treated with ERT |
| Symptomatic disease, including manifestations of abdominal or bone pain, fatigue, exertional limitations, weakness, and cachexia | |
| Growth failure | |
| Any evidence of skeletal involvement, including Erlenmeyer flask deformity (EFD) | |
| Platelet count ≤ 60,000 $mm^3$ and/or documented abnormal bleeding episode(s) | |
| Hemoglobin ≤ 2.0 g/dL below lower limit of normal for age and sex | |
| Impaired quality of life (QOL) due to Gaucher disease | |

- Generally, the recommended initial imiglucerase dose children at increased risk is 60 units/kg body weight every 2 weeks.
- Insufficient information is available concerning dose reduction in the pediatric population.

Genetics In Medicine. Individualization of long-term enzyme replacement therapy for Gaucher disease. *Hans C. Andersson, Joel Charrow, Paige Kaplan, Pramod Mistry, Gregory M. Pastores, Ainu Prakesh-Cheng, Barry E. Rosenbloom, and Neal J. Weinreb, for the International Collaborative Gaucher Group U.S. Regional Coordinators.* February 2005, Vol. 7: No. 2

# Starting doses?

Adults

When?

**Table 2**
Adults with Gaucher disease: Risk assessment

| Increased risk | Lower risk |
|---|---|
| One or more of the following: | Level of disease meets ALL of the following: |
| Symptomatic skeletal disease | Normal liver, cardiac, lung and renal functions<br>Minimal impairment of QOL<br>No obvious or recent rapid progression of disease manifestations<br>Skeletal disease limited to mild osteopenia and Erlenmeyer flask deformity<br>Hemoglobin > 10.5 g/dL for females and > 11.5 g/dL for males (or not more than 2.0 g/dL below lower limit of normal for age and sex)<br>Platelet count > 60,000 $mm^3$ on three determinations<br>Liver volume < 2.5 × normal<br>Spleen volume < 15 × normal |
| Moderate to severe osteopenia | |
| Chronic bone pain | |
| Bone crises | |
| Avascular necrosis | |
| Pathological fractures | |
| Joint replacement(s) | |
| Impaired QOL due to Gaucher disease | |
| Cardiopulmonary disease, including pulmonary hypertension | |
| Platelet count ≤ 60,000 $mm^3$ or documented abnormal bleeding episodes | |
| Symptomatic anemia or hemoglobin ≤ 8.0 g/dL | |
| Transfusion dependency | |
| Significant liver disease | |
| Hepatomegaly that is 2.5 × normal | |
| Infarcts | |
| Portal hypertension | |
| Hepatitis | |
| Significant splenic disease | |
| Splenomegaly that is ≥ 15 × normal | |
| Infarcts | |
| Significant renal disease | |
| Any concomitant medical condition that further complicates or exacerbates Gaucher disease or its signs and symptoms | |

Generally, the recommended initial imiglucerase dose in adults:

- Increased risk is 60 units/kg body weight every 2 weeks.
- Lower risk adults is 30 to 45 units/kg every 2 weeks.

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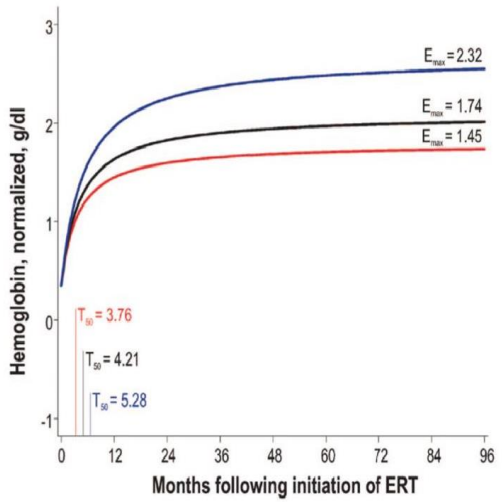
# Dose – response relationship for ERT with Cerezyme in patients with GD Type 1

When?

PC: Fold increase

A

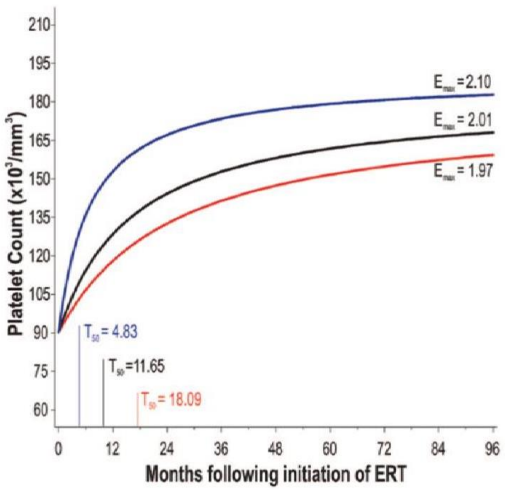



B

| Parameter | Hemoglobin, normalized, g/dL | 95% CI | | p-value* |
|---|---|---|---|---|
| $E_{max}$ | Absolute change from baseline | | | |
| 48 to <75 U/kg/2wk | 2.32 | 2.13 | 2.51 | <0.01 |
| 29 to <48 U/kg/2wk | 1.74 | 1.61 | 1.85 | |
| 5 to <29 U/kg/2wk | 1.45 | 1.27 | 1.61 | |
| $T_{50}$ | Months | | | |
| 48 to <75 U/kg/2wk | 5.28 | 3.90 | 7.14 | 0.28 |
| 29 to <48 U/kg/2wk | 4.21 | 3.17 | 5.62 | |
| 5 to <29 U/kg/2wk | 3.76 | 2.41 | 5.91 | |

*p-value indicates statistical significance among dosing groups.

A

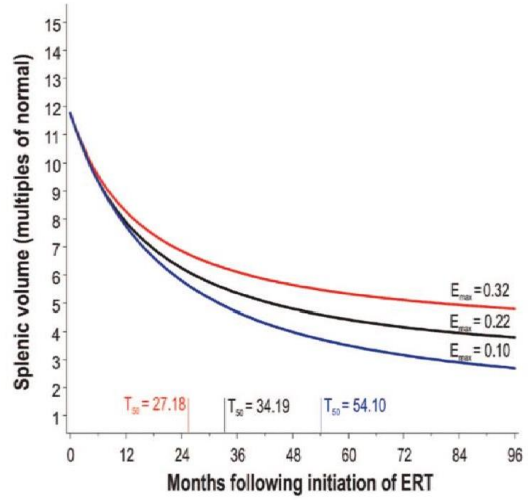



B

| Parameter | Platelet Counts | 95% CI | | p-value* |
|---|---|---|---|---|
| $E_{max}$ | Relative change from baseline | | | |
| 48 to <75 U/kg/2wk | 2.10 | 1.99 | 2.21 | 0.13 |
| 29 to <48 U/kg/2wk | 2.01 | 1.95 | 2.08 | |
| 5 to <29 U/kg/2wk | 1.97 | 1.87 | 2.07 | |
| $T_{50}$ | Months | | | |
| 48 to <75 U/kg/2wk | 4.83 | 3.74 | 6.22 | <0.01 |
| 29 to <48 U/kg/2wk | 11.65 | 9.66 | 14.04 | |
| 5 to <29 U/kg/2wk | 18.09 | 13.39 | 24.44 | |

*p-value indicates statistical significance among dosing groups.

A

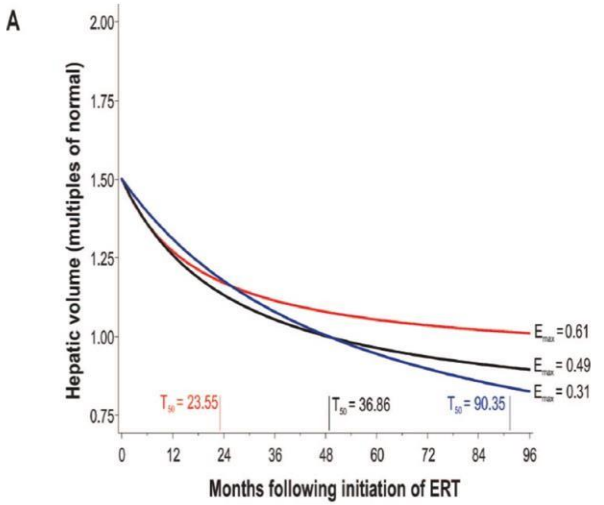



B

| Parameter | Splenic Volume | 95% CI | | p-value* |
|---|---|---|---|---|
| $E_{max}$ | Relative change from baseline | | | |
| 48 to <75 U/kg/2wk | 0.10 90% | 0.07 | 0.14 | <0.01 |
| 29 to <48 U/kg/2wk | 0.22 78% | 0.19 | 0.24 | |
| 5 to <29 U/kg/2wk | 0.32 68% | 0.27 | 0.37 | |
| $T_{50}$ | Months | | | |
| 48 to <75 U/kg/2wk | 54.10 | 30.01 | 97.51 | 0.10 |
| 29 to <48 U/kg/2wk | 34.19 | 26.31 | 44.42 | |
| 5 to <29 U/kg/2wk | 27.18 | 18.43 | 40.07 | |

*p-value indicates statistical significance among dosing groups.

A




B

| Parameter | Hepatic Volume | 95% CI | | p-value* |
|---|---|---|---|---|
| $E_{max}$ | Relative change from baseline | | | |
| 48 to <75 U/kg/2wk | 0.31 69% | 0.24 | 0.40 | <0.01 |
| 29 to <48 U/kg/2wk | 0.49 51% | 0.45 | 0.53 | |
| 5 to <29 U/kg/2wk | 0.61 39% | 0.56 | 0.67 | |
| $T_{50}$ | Months | | | |
| 48 to <75 U/kg/2wk | 90.35 | 50.82 | 160.64 | <0.01 |
| 29 to <48 U/kg/2wk | 36.86 | 23.88 | 56.91 | |
| 5 to <29 U/kg/2wk | 23.55 | 13.57 | 40.86 | |

*p-value indicates statistical significance among dosing groups.

Dose-response relationships for enzyme replacement therapy with imiglucerase/alglucerase in patients with Gaucher disease type 1. Gregory A. Grabowski, Katherine Kacena, P.Alexander Cole, Carla Hollak, Lin Zhang, John Yee, Pramod K. istry, Ari Zimran, Joel Charrow and Stephan vom Dahl. Genet Med. 2009 February ; 11(2): 92–100.

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# Dose – response relationship for ERT with Cerezyme in patients with GD Type 1

When?

Retrospectively comparison of long-term outcome of ERT at 2 large European treatment centers,

- AMC, The Netherlands (n=49, median dose, 15-30 U/kg/4 wks)
- HHU, Germany (n= 57, median dose, 80 U/kg/4 wks).

All follow-up parameters were matched separately at baseline.

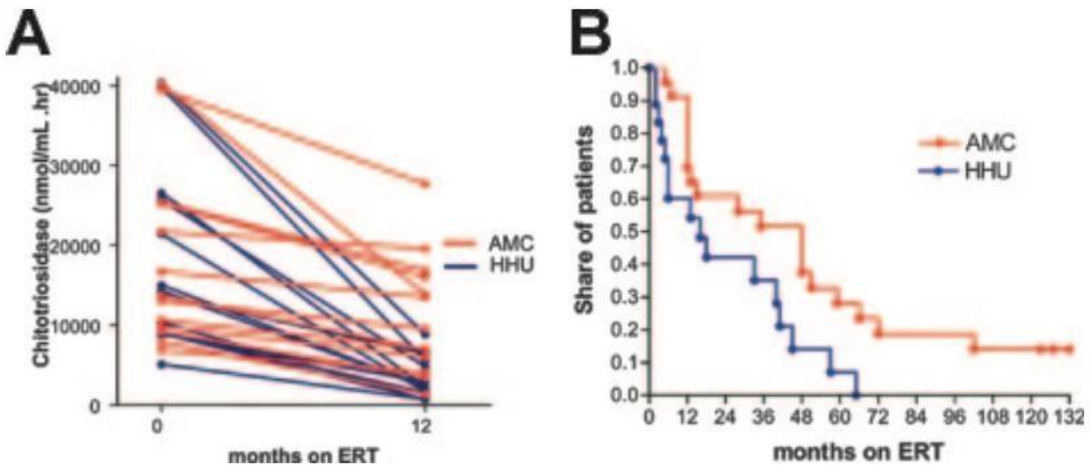


**Figure 3. Impact of ERT on changes on plasma chitotriosidase activity.** (A) Plasma chitotriosidase at baseline and after 12 months, (B) time to reach a chitotriosidase of less than 5000 nmol/mL/h. Chitotriosidase levels of carriers of the chitotriosidase null mutation were multiplied by 2.[29]


1. Dose-response relationships for enzyme replacement therapy with imiglucerase/alglucerase in patients with Gaucher disease type 1. Gregory A. Grabowski, Katherine Kacena, P. Alexander Cole, Carla Hollak, Lin Zhang, John Yee, Pramod K. istry, Ari Zimran, Joel Charrow and Stephan vom Dahl. Genet Med. 2009 February ; 11(2): 92–100.
2. Superior effects of high-dose enzyme replacement therapy in type 1 Gaucher disease on bone marrow involvement and chitotriosidase levels: a 2-center retrospective analysis. Carla E. M. Hollak, Mario Maas, Ludger W. Poll, and Stephan vom Dahl. Blood, 1 August 2006. Volume 108, number 3.

# Dose – response relationship for ERT with Cerezyme in patients with GD Type 1

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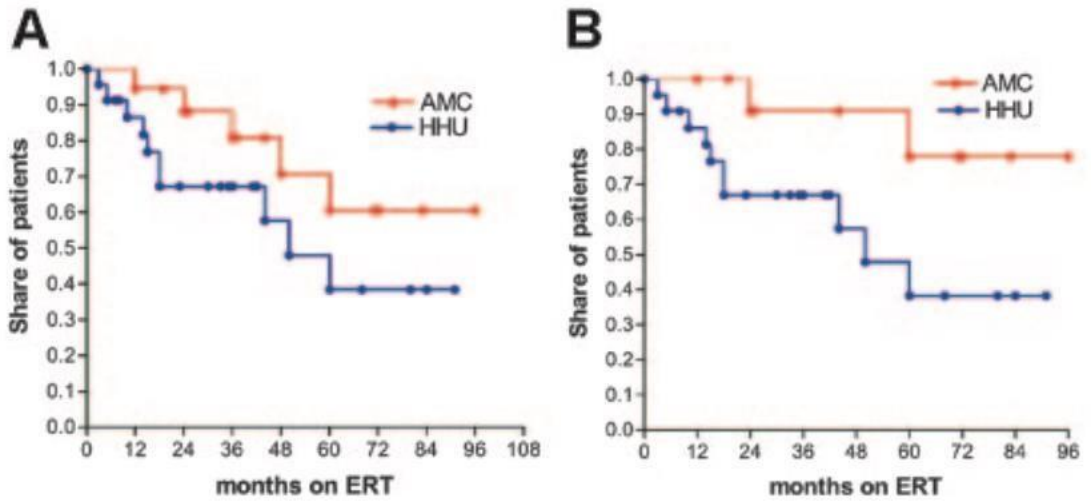


**Figure 4. Impact of ERT on changes in bone marrow burden score.** (A) Time to reach a decrease of 2 points in BMB score, as measured by MRI, from baseline of patients with a baseline BMB of 2 to 8, (B) time to reach a decrease of 2 points in BMB score from baseline of patients with a baseline BMB of 6 to 8.


1. Dose-response relationships for enzyme replacement therapy with imiglucerase/alglucerase in patients with Gaucher disease type 1. Gregory A. Grabowski, Katherine Kacena, P. Alexander Cole, Carla Hollak, Lin Zhang, John Yee, Pramod K. istry, Ari Zimran, Joel Charrow and Stephan vom Dahl. Genet Med. 2009 February ; 11(2): 92–100.
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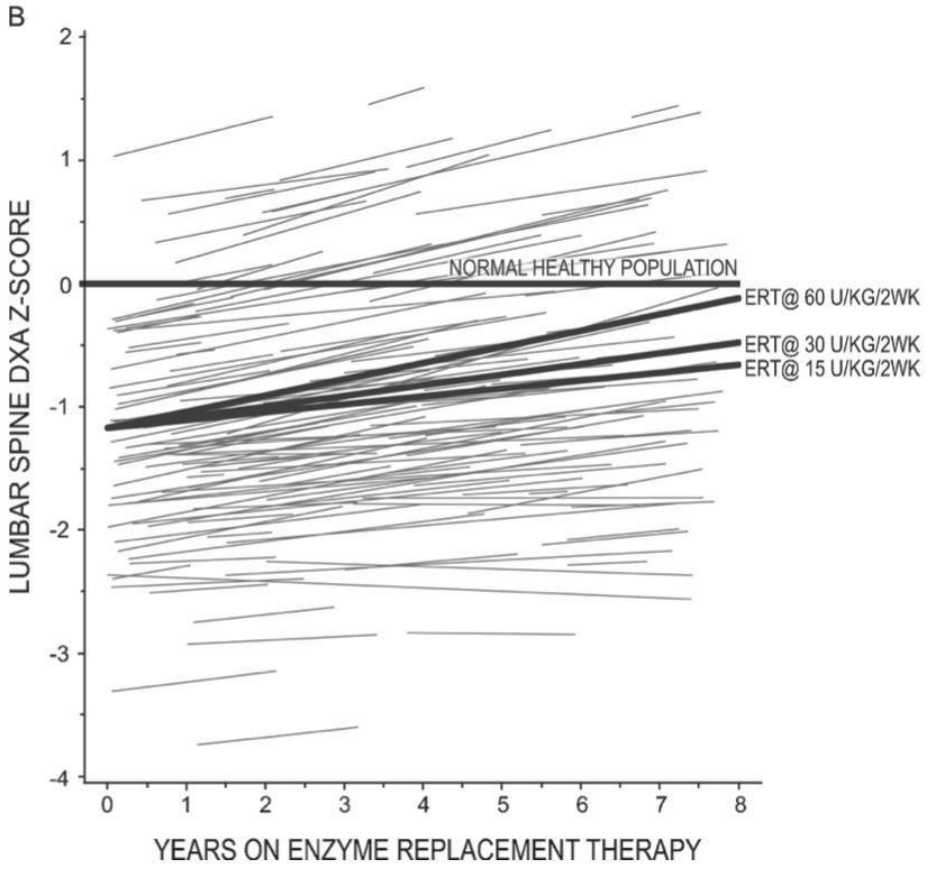
When?

## Dose – response relationship for ERT with Cerezyme in patients with GD Type 1

ERT with imiglucerase may significantly reverse decreases in lumbar spine BMD in a dose-dependent manner. However, the time required to achieve a normal BMD is usually longer than the time required to attain therapeutic goals for the hematological and visceral aspects of GD.




3. Effect of Enzyme Replacement Therapy With Imiglucerase on BMD in Type 1 Gaucher Disease. Richard J Wenstrup, Katherine A Kacena, Paige Kaplan, Gregory M Pastores, Ainu Prakash-Cheng, Ari Zimran, and Thomas N Hangartne. J Bone Miner Res 2007;21:119–126. Published online on October 9, 2006.

# AGENDA

**Therapeutic Opportunities according to therapeutic objectives in Gaucher Disease**

**Therapeutic Objetives =**

5. Therapeutic Objetictives = Therapeutics Goals (TGs)

# Monitoreo de las MTs

TGs

**Table 4**
Essential recommended assessments for Gaucher disease type 1 patients with asterisks indicating assessments specific to eliglustat.

| | Baseline | Year 1 | Long Term |
|---|---|---|---|
| History | | | |
| Cardiac, renal, and hepatic status | Yes | At each visit or with significant changes in disease status | At each visit or with significant changes in disease status |
| Pregnancy, intent to become pregnant, and lactation* | Yes | At each visit | At each visit |
| Medications | | | |
| Concomitant medications* (including grapefruit) with regard to CYP2D6, CYP3A, and P-gp substrate metabolism | Yes | At each visit or with significant changes in disease status | At each visit or with significant changes in disease status |
| Medication adherence* | Yes (assess ability to adhere) | At each visit or with significant changes in disease status | At each visit or with significant changes in disease status |
| Blood | | | |
| Complete blood count (i.e., monitoring of hemoglobin and platelets) | Yes | Every 3 months | Every 6–12 months (or as clinically indicated) to assess against therapeutic goals |
| Biomarkers (CCL18 if available, chitotriosidase, TRAP, ACE) | Yes | Every 3 months | Every 6–12 months or as clinically indicated |
| CYP2D6 metabolizer profile* | Yes | Not applicable | Not applicable |
| Hepatic function (should include AST, ALT, AP, bilirubin, albumin) | Yes | Annually | Annually |
| PT/PTT | Yes | Annually | Annually |
| Renal function – should include BUN, creatinine, eGFR | Yes | Annually | Annually |
| Electrolytes | Yes | Annually | Annually |
| Imaging | | | |
| Spleen and liver volumes (MRI preferred) | Yes | Annually | Annually |
| MRI (coronal; T1- and T2-weighted) of the entire femora | Yes | Annually | Annually |
| X-ray: AP of femora and lateral of spine | Yes | As clinically indicated | As clinically indicated |
| DEXA (hip and spine) | Yes | NA | Every 2 years or as clinically indicated |
| ECG | Yes | As clinically indicated | As clinically indicated |

ACE: angiotensin converting enzyme; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AP: alkaline phosphatase; BUN: blood urea nitrogen; CCL 18: chemokine (C-C motif) ligand 18; DEXA: dual-energy X-ray absorptiometry; ECG: electrocardiogram; GFR: glomerular filtration rate; MRI: magnetic resonance imaging; PT: prothrombin time; PTT: partial thromboplastin time; TRAP: tartrate resistant acid phosphatase.

* These assessments are considered essential for monitoring patients with Gaucher disease type 1 on eliglustat therapy. Additional tests that may be useful in the care of patients with Gaucher disease type 1 are discussed in the text. Recommendations for comprehensive evaluation and monitoring of patients with Gaucher disease type 1 have been published elsewhere

Molecular Genetics and Metabolism. Recommendations for the use of eliglustat in the treatment of adults with Gaucher disease type 1 in the United States. Manisha Balwani , Thomas Andrew Burrow , Joel Charrow , Ozlem Goker-Alpan , Paige Kaplan, Priya S. Kishnani, Pramod Mistry, Jeremy Ruskin, Neal Weinreb

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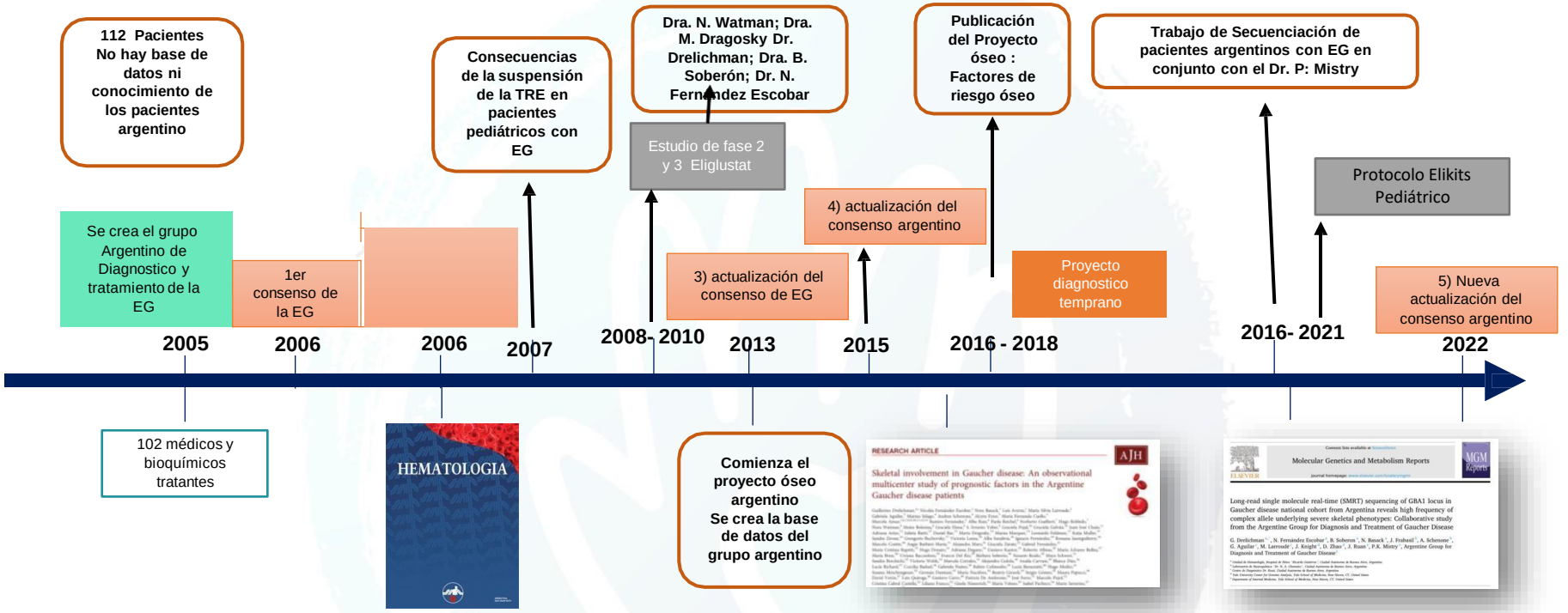
# GRUPO ARGENTINO DE EG: 54 PUBLICACIONES ENTRE REVISTAS CIENTIFICAS Y CONGRESOS NACIONALES E INTERNACIONALES

TGs




2005: 112 Pacientes — 2022: Registro 259 Argentina


G. Drelichman et al. Consecuencias de la suspensión de la TRE J. of Pediatr 207 G. Drelichman et al . HEMATOLOGÍA • Volumen 17 - Suplemento Enfermedad de Gaucher: 25 - 60, 2013 G. Drelichman et al. Actualización del consenso argentino. HEMATOLOGÍA Volumen 19 Suplemento Enfermedad de Gaucher: 4 – 51, 2015 G. Drelichman et al. Am J Hematol. 2016 Oct; 91(10):E448-53. doi: 10.1002/ajh.24486. Epub 2016 Aug 22. Timothy Cox et al Eliglustat maintains long-term clinical stability in patients with Gaucher disease type 1 stabilized on enzyme therapy Blood 2017 Heather Lau Etr al. Long-term treatment response based on severity of Gaucher disease type 1 at baseline after 8 years of treatment with oral eliglustat: Final efficacy and safety results from a phase 2 clinical trial in treatment-naïve adult patients Dra. Elena Leukina M Eliglustat, an investigational oral therapy for Gaucher disease type 1: Phase 2 trial results after 4 years of treatment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**Therapeutic Objectives?**

TGs

ELSEVIER

*Seminars in* HEMATOLOGY

# Therapeutic Goals in the Treatment of Gaucher Disease

Gregory M. Pastores,[a] Neal J. Weinreb,[b] Hans Aerts,[c] Generoso Andria,[d] Timothy M. Cox,[e] Manuel Giralt,[f] Gregory A. Grabowski,[g] Pramod K. Mistry,[h] and Anna Tylki-Szymańska[i]

TGs

## Therapeutic Objectives?

**Table 1 Therapeutic Goals for Anemia**

- Increase hemoglobin levels within 12 to 24 months to
  - ≥11.0 g/dL for women and children
  - ≥12.0 g/dL for men
- Eliminate blood transfusion dependency
- Reduce fatigue, dyspnea, angina
- Maintain improved Hb values achieved after the first 12 to 24 months of therapy

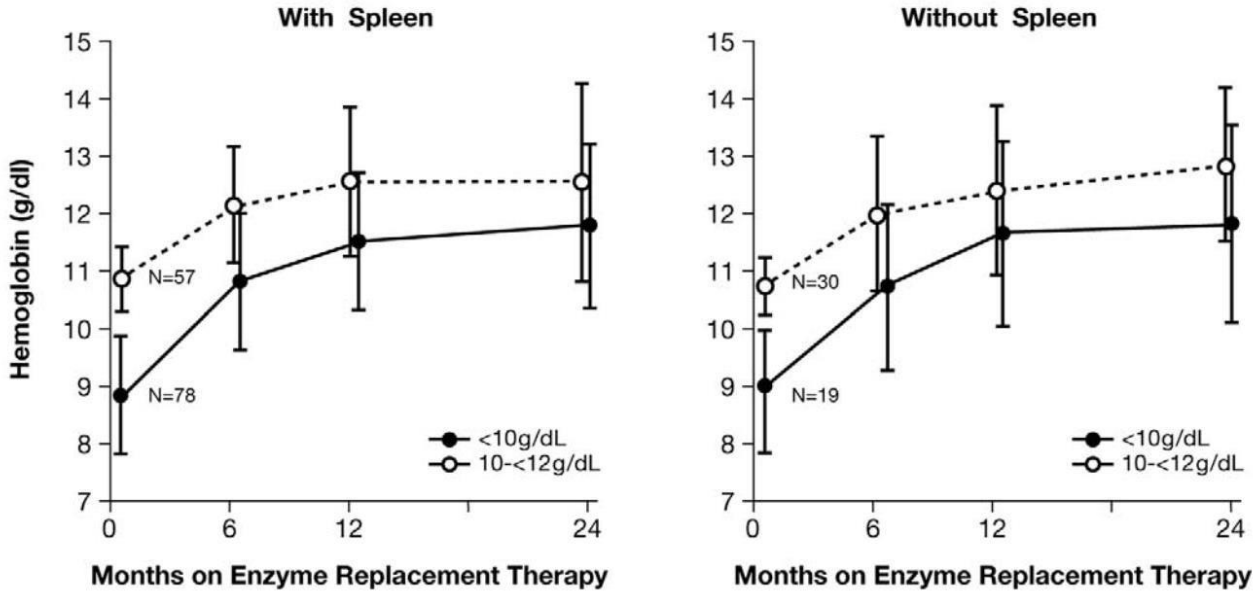


**Figure 1** Changes in hemoglobin concentration during the first 2 years of ERT among patients in the ICGG Gaucher Registry. Reprinted with permission from Excerpta Medica.[9]

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## Therapeutic Objectives?

**Table 2** Therapeutic Goals for Thrombocytopenia

- All patients: increase platelet counts during the first year of treatment sufficiently to prevent surgical, obstetrical, and spontaneous bleeding.
- Patients with splenectomy: normalization of platelet count by 1 year of treatment
- Patients with an intact spleen:
  - Moderate baseline thrombocytopenia: the platelet count should increase by 1.5- to 2.0-fold by year 1 and approach low-normal level by year 2
  - Severe baseline thrombocytopenia: the platelet count should increase by 1.5-fold by year 1 and continue to increase slightly during years 2 to 5 (doubling by year 2), but normalization is not expected
  - Avoid splenectomy (may be necessary during life-threatening hemorrhagic events)
  - Maintain stable platelet counts to eliminate risks of bleeding after a maximal response has been achieved

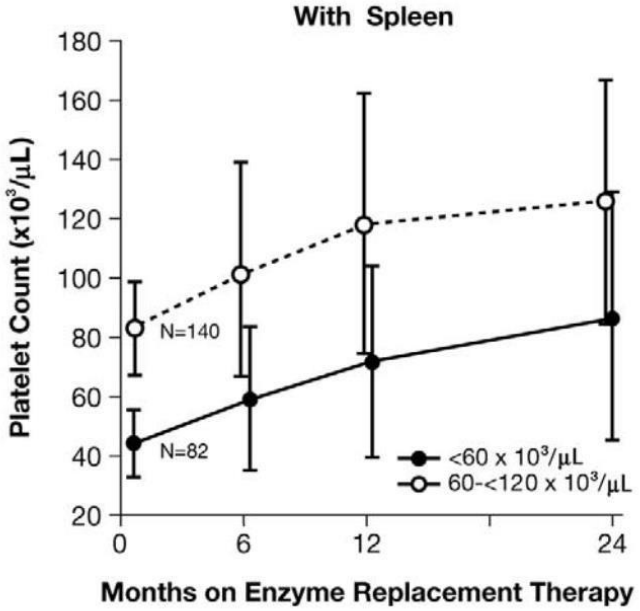
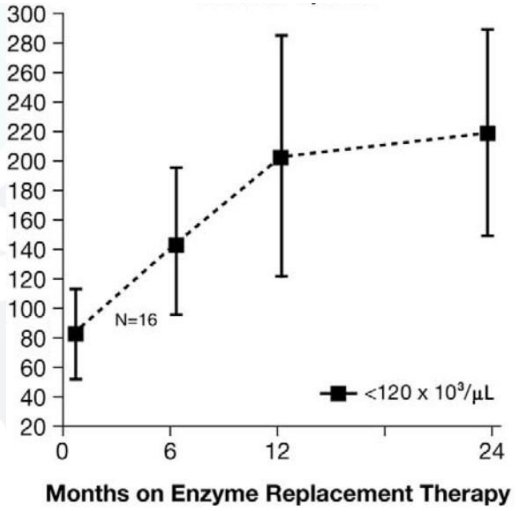



**Figure 2** Changes in platelet counts during the first 2 years Reprinted with permission from Excerpta Medica.[9]




ERT among patients in the ICGG Gaucher Registry.

TGs

**Table 3** Therapeutic Goals for Hepatomegaly

- Reduce and maintain the liver volume to 1.0 to 1.5 times normal
- Reduce the liver volume by 20% to 30% within year 1 to 2 and by 30% to 40% by year 3 to 5

**Table 4** Therapeutic Goals for Splenomegaly

- Reduce and maintain spleen volume to ≤2 to 8 times normal
- Reduce the spleen volume by 30% to 50% within year 1 and by 50% to 60% by year 2 to 5
- Alleviate symptoms due to splenomegaly: abdominal distension, early satiety, new splenic infarction
- Eliminate hypersplenism

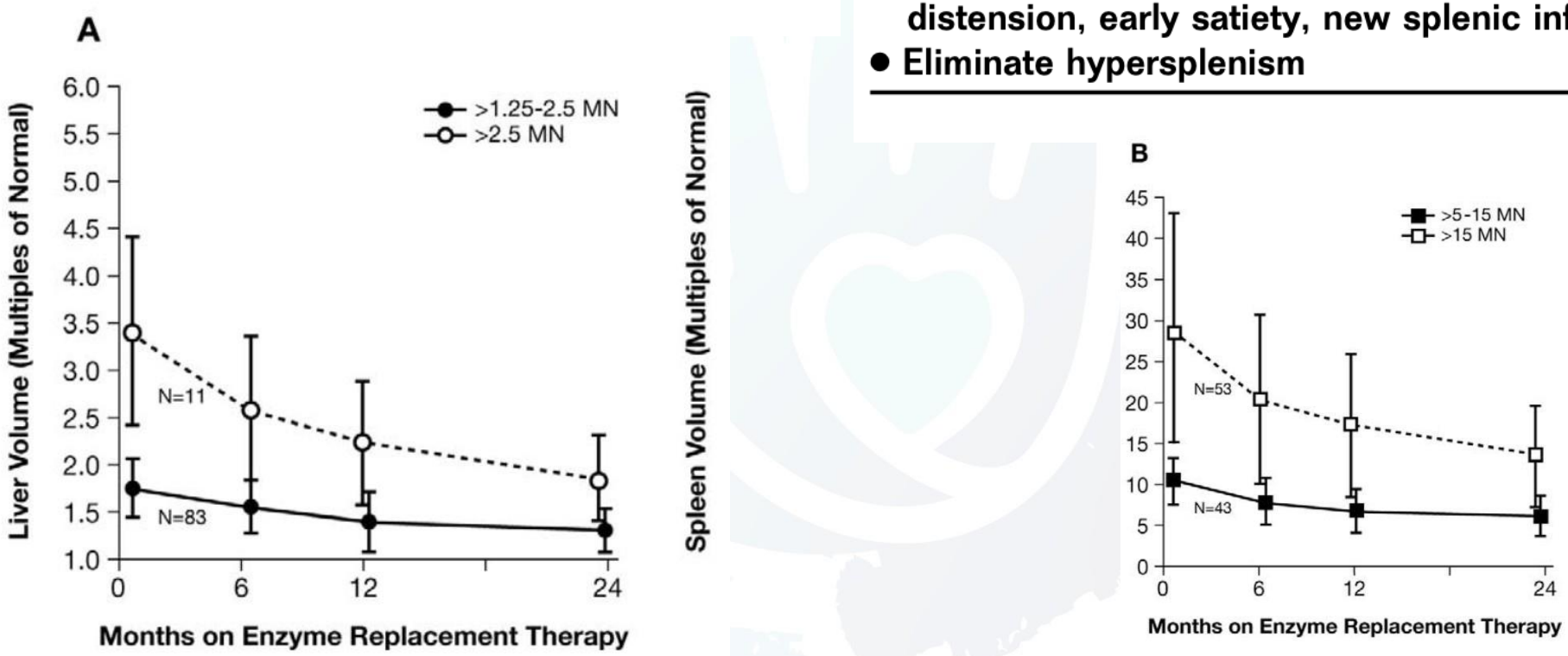



**Figure 3** Changes in liver volume (A, patients with spleen) and spleen volume (B) according to baseline size during the first 2 years of ERT for patients in the ICGG Gaucher Registry. Reprinted with permission from Excerpta Medica.[9]

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## Table 5 Therapeutic Goals for Skeletal Pathology

- Lessen or eliminate bone pain within 1 to 2 years
- Prevent bone crises
- Prevent osteonecrosis and subchondral joint collapse
- Improve BMD
  - Pediatric patients
    - Attain normal or ideal peak skeletal mass
    - Increase cortical and trabecular BMD by year 2
  - Adult patients
    - Increase trabecular BMD by 3 to 5 years

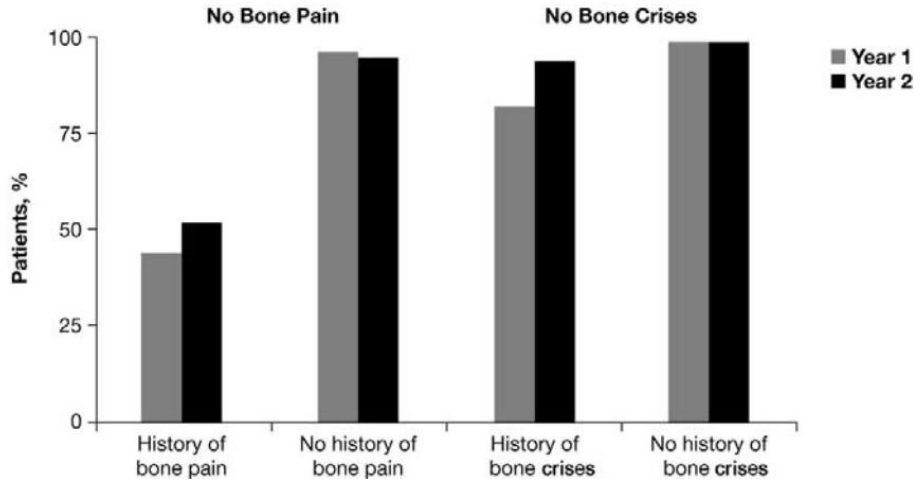


**Figure 4** Bone pain and bone crises among patients in the ICGG Gaucher Registry receiving ERT for 2 years according to previous history of bone pain and bone crises. Reprinted with permission from Excerpta Medica.[9]

## Table 6 Therapeutic Goals for Growth in Pediatric Patients

- Normalize growth such that patient achieves a normal height according to population standards within 3 years of treatment.
- Achieve normal onset of puberty

## Table 7 Therapeutic Goals for Pulmonary Involvement

- Reverse hepatopulmonary syndrome and dependency on oxygen
- Ameliorate pulmonary hypertension (ERT plus adjuvant therapies)
- Improve functional status and quality of life
- Prevent rapid deterioration of pulmonary disease and sudden death
- Prevent pulmonary disease by timely initiation of ERT and avoidance of splenectomy

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# TGs for patients with GD

## Short Term TGS

- **Reduce bone pain** (not related to irreversible bone disease) within 1–2 years
- **Decrease BM involvement** in patients without severe, irreversible disease
- **Increase BMD by 2 years in adult patients** with a T-score **below -2.5** at baseline
- Attain **normal** or **ideal peak skeletal mass** in **children**
- **Normalize growth** in line with target height within 2 years of treatment

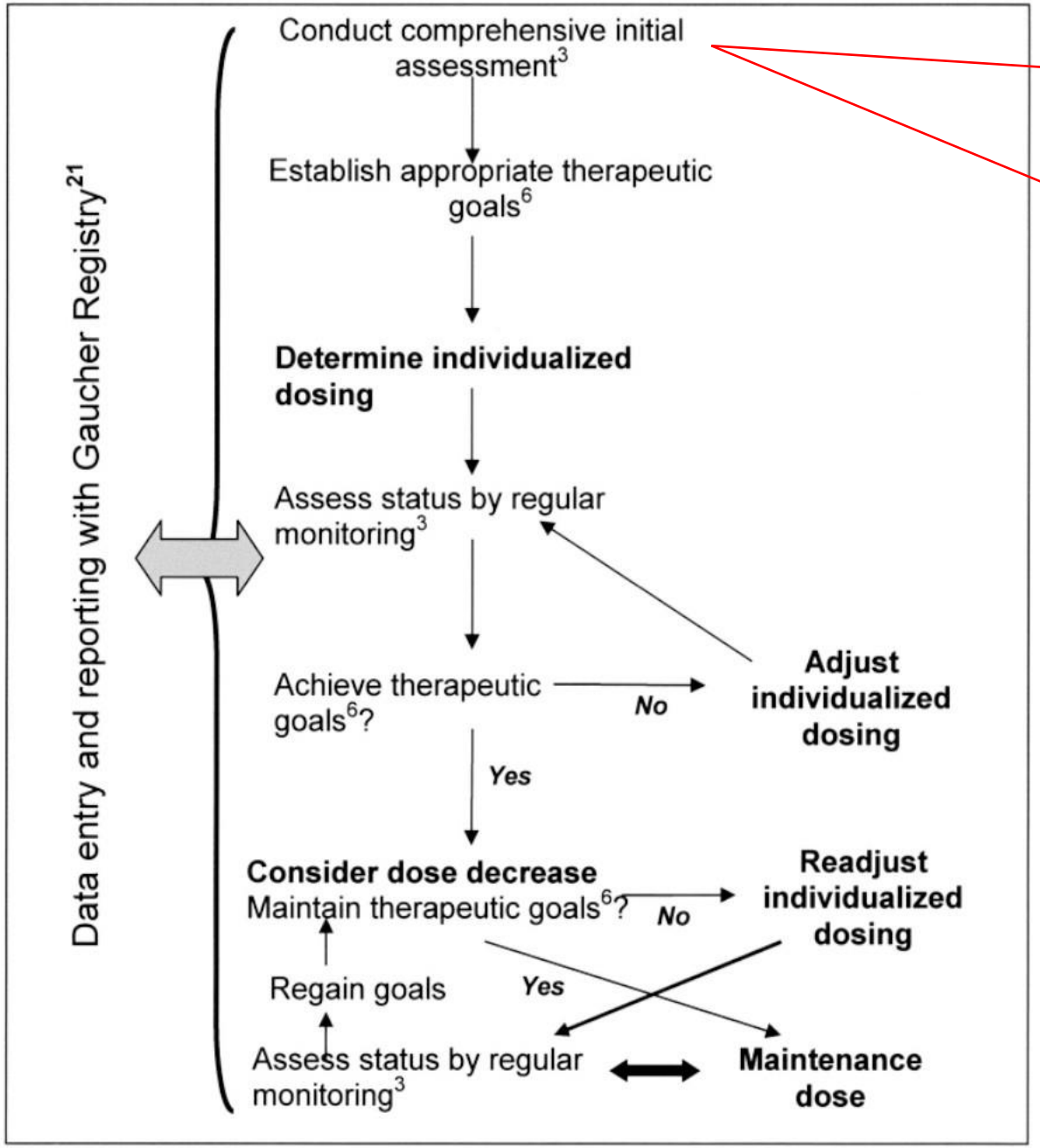
## Lonf Term TGS

- **Prevent bone complications** (e.g. AVN, bone infarcts, bone crises)
- **Prevent osteopenia and osteoporosis** (maintain BMD T-scores above -1)
- **Prevent chronic use of analgesic medication for bone pain**
- **Maintain normal mobility** (or improve mobility if impaired at baseline)
- **Increase physical activity**

AVN, avascular necrosis; BM, bone marrow; BMD, bone mineral density

Biegstraaten M *et al. Blood Cells Mol Dis* 2018;68:203

**ERT**
**Dose**
**Optimization**




Ped or adult?

High or low risk?

TGs
Dose

Genetics In Medicine. Individualization of long-term enzyme replacement therapy for Gaucher disease. *Hans C. Andersson, Joel Charrow, Paige Kaplan, Pramod Mistry, Gregory M. Pastores, Ainu Prakesh-Cheng, Barry E. Rosenbloom, and Neal J. Weinreb, for the International Collaborative Gaucher Group U.S. Regional Coordinators.* February 2005, Vol. 7: No. 2

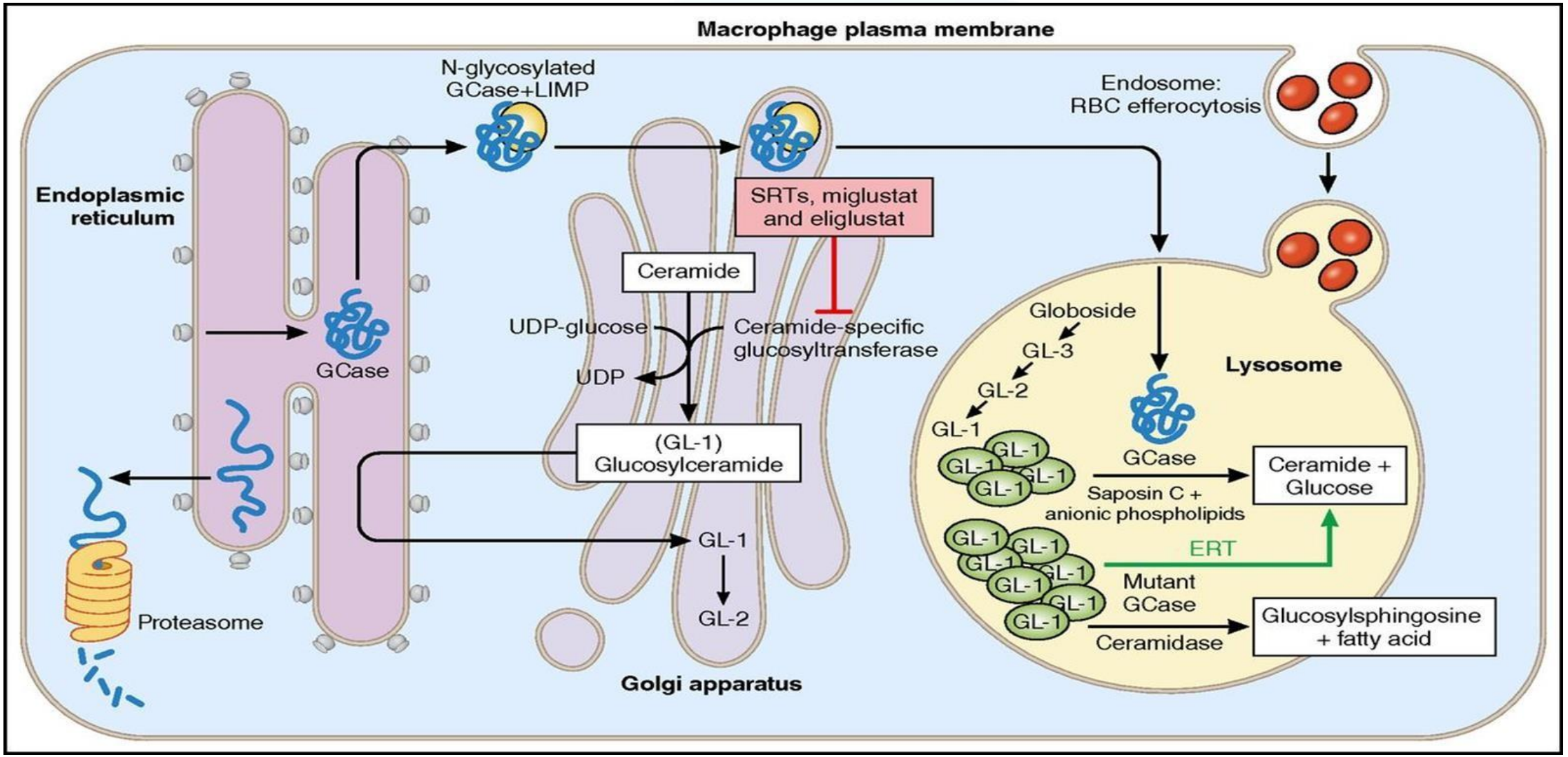
# AGENDA

**Therapeutic Opportunities according to therapeutic objectives in Gaucher Disease**

**Therapeutic Objetives =**

# Substrate Reduction: ERT and Substrate Synthesis Inhibition Therapy



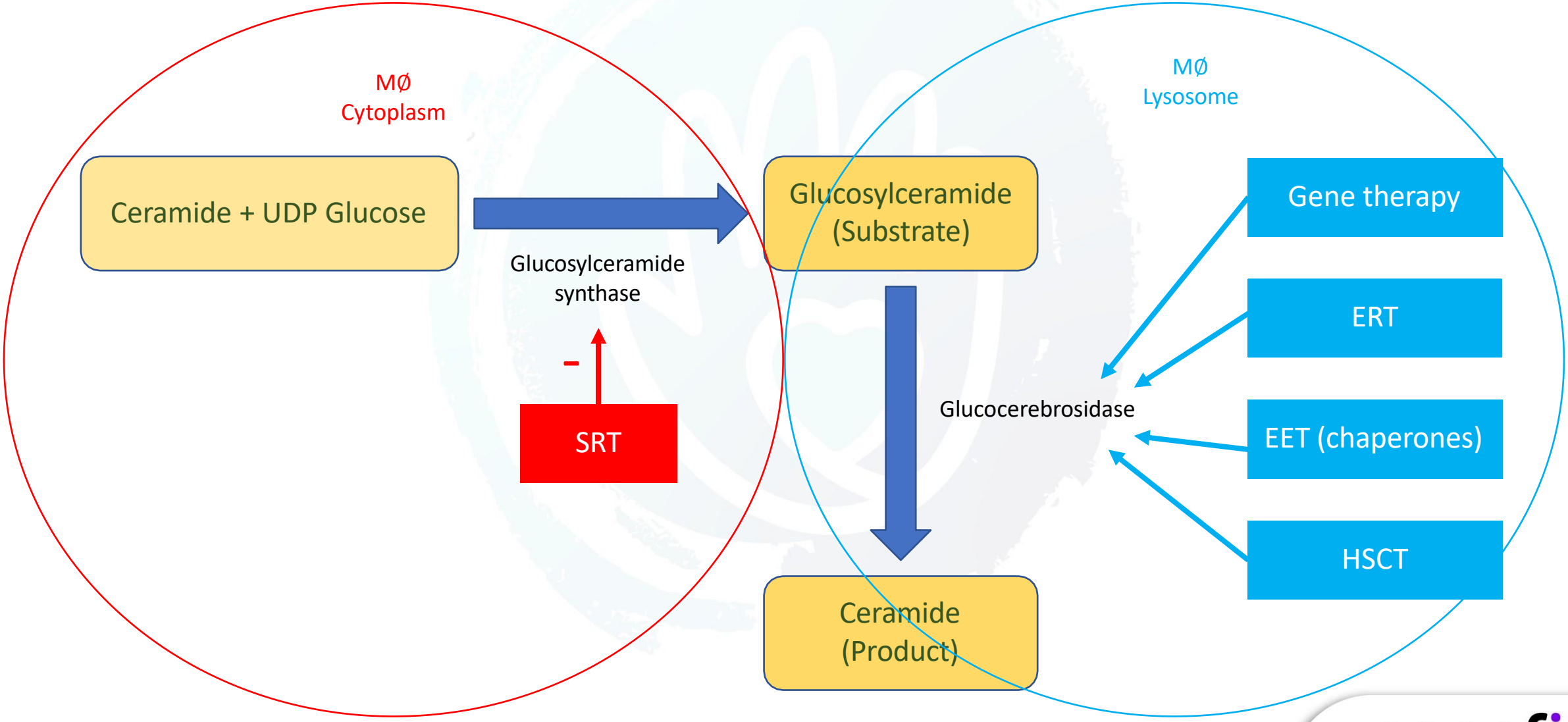



Weinreb, NJ. Encore! Oral therapy for type 1 Gaucher disease. Blood. 2017;129:2337-2338.

# Que tratamientos tenemos?

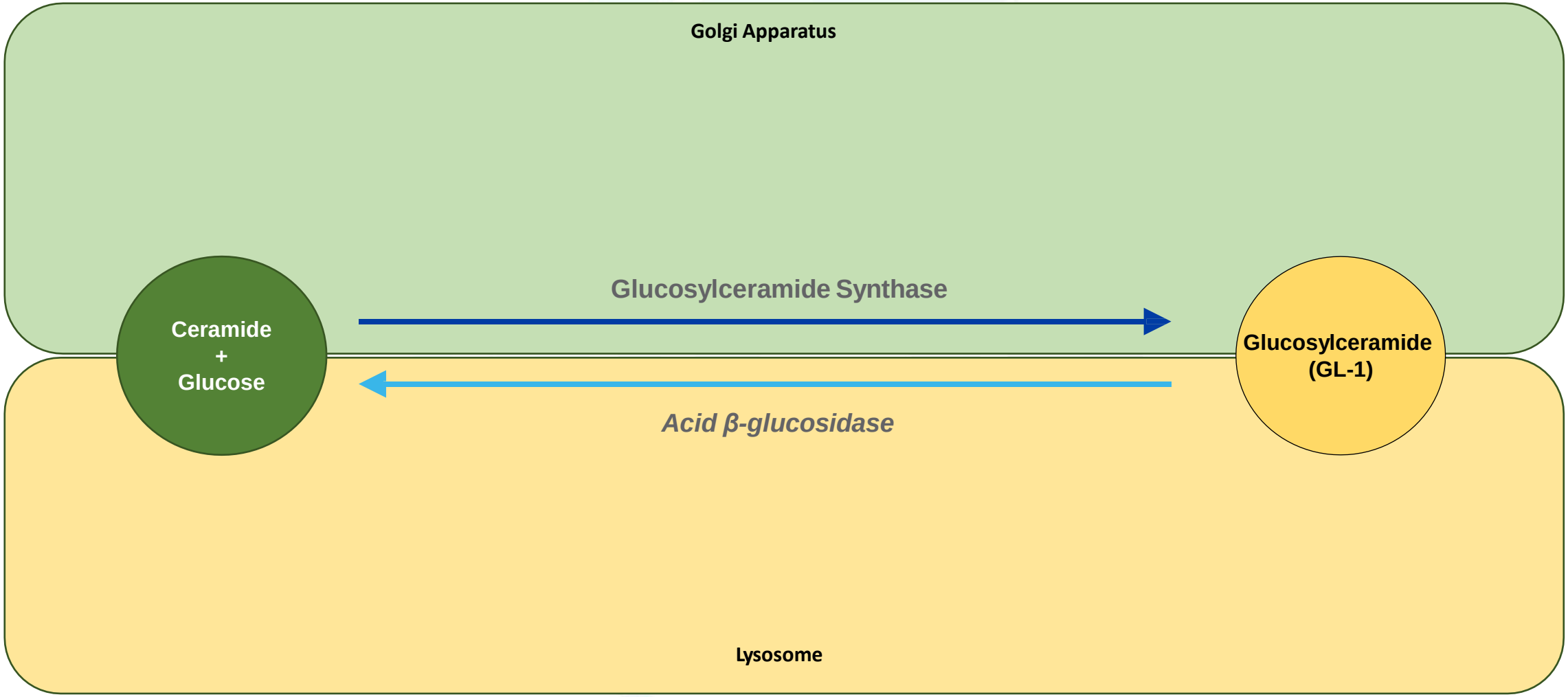
Options

Estrategias de acuerdo a la fisiopatología de la EG



# Normal balance between substrate synthesis and degradation

Options




GL-1 synthase=glucosylceramide synthase. Figure is adapted from Shayman JA. *Drugs Future*. 2010;35:613-620.


1. Cerdelga Summary of Product Characteristics (SmPC); Genzyme Europe B.V.; January 2020.
2. Shayman JA. *Drugs Future*. 2010;35:613-620.
3. Mistry PK, et al. *Am J Hematol*. 2011;86(1):110-115.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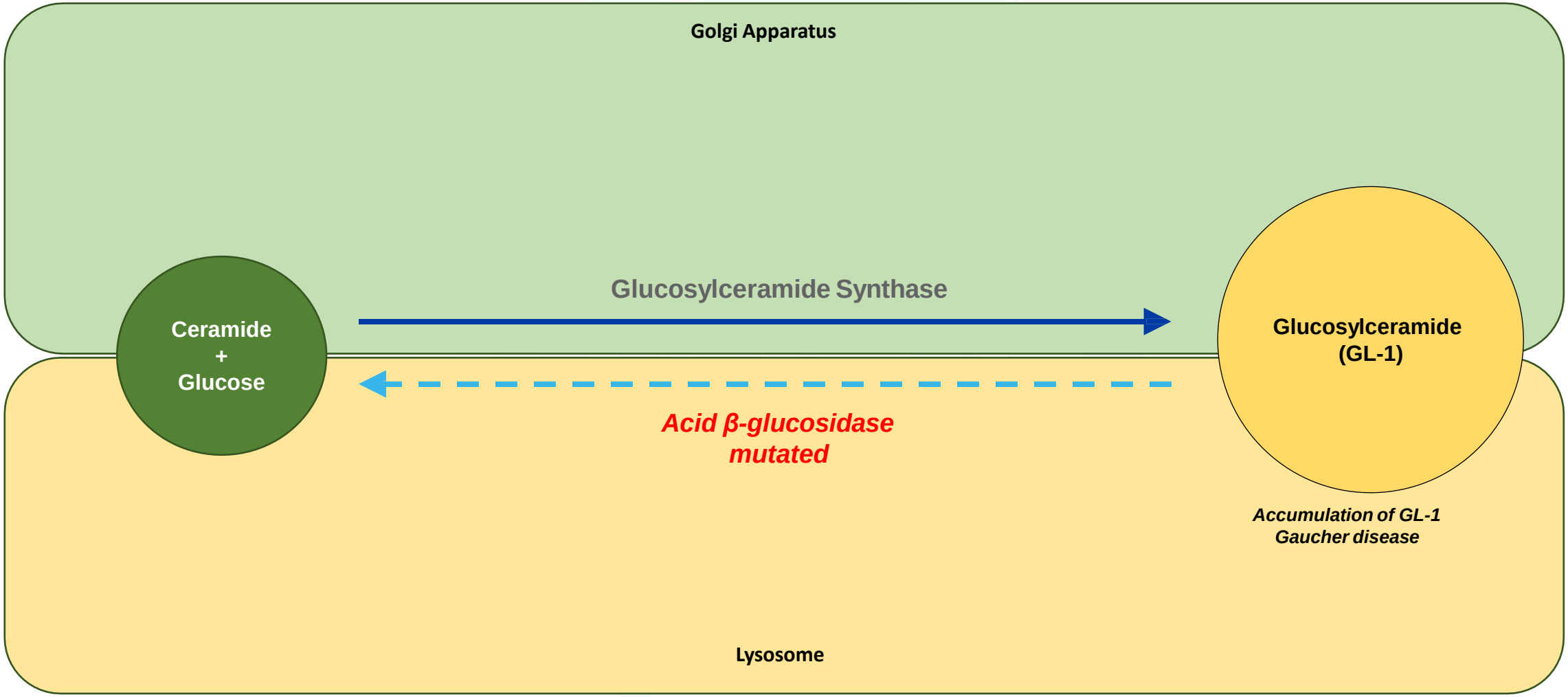
# Balance Between Substrate Synthesis and Degradation in GD

Options

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2. Shayman JA. *Drugs Future*. 2010;35:613-620.
3. Mistry PK, et al. *Am J Hematol*. 2011;86(1):110-115.


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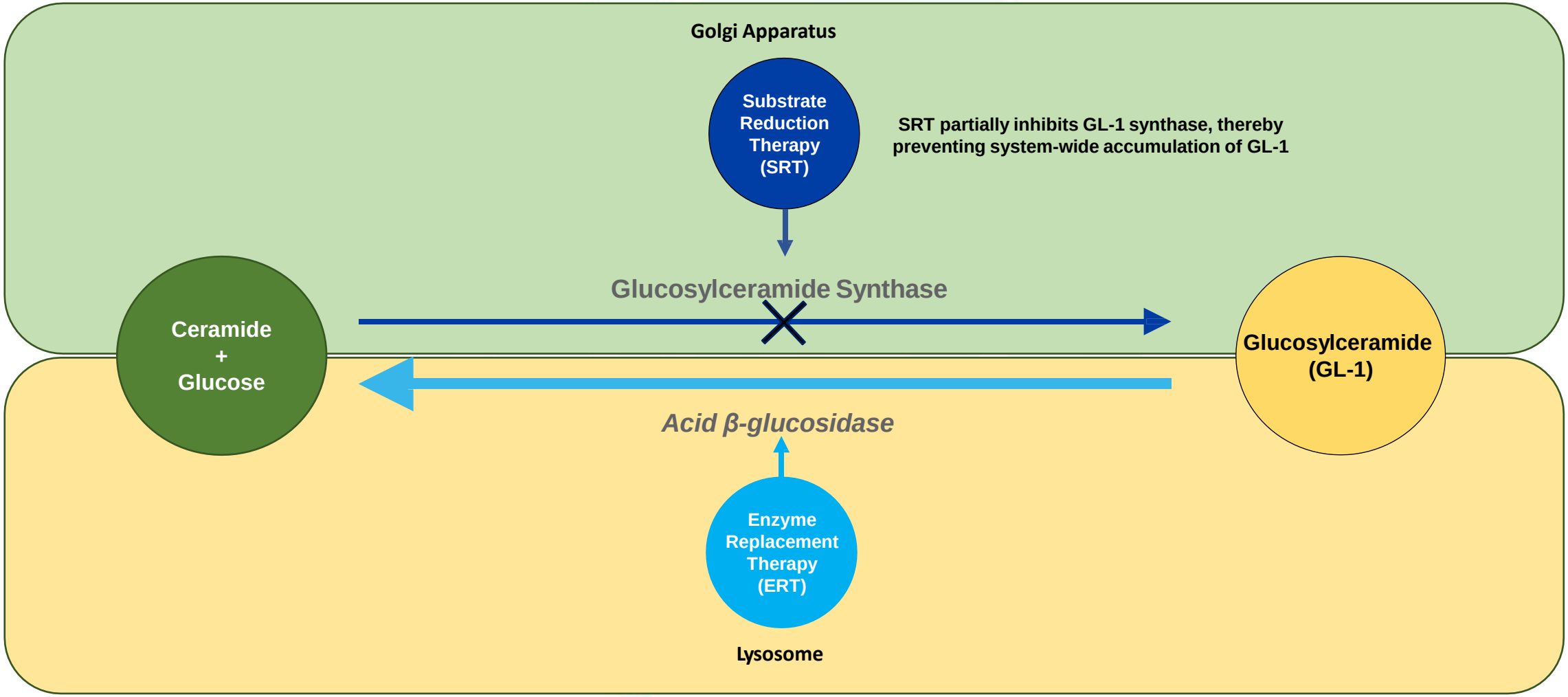
# SRT and ERT - Synthesis and Degradation

Options

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3. Mistry PK, et al. *Am J Hematol*. 2011;86(1):110-115.


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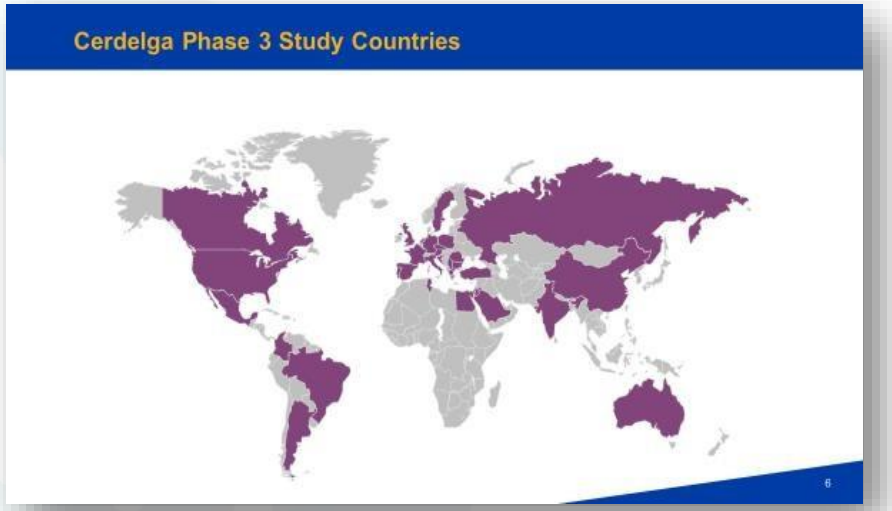
# Cerdelga: First-Line Oral Therapy for Adult Patients With Gaucher Disease Type 1

Options

- Proven safety and efficacy supported by one 8-year long-term Phase 2 study, two pivotal Phase 3 studies (ENGAGE and ENCORE), and one supplemental dose frequency Phase 3b study (EDGE)[1-5]
- Nearly 400 patients including treatment-naïve and patients previously stabilized on ERT
  - 29 Countries
  - 1400 person-years of Cerdelga exposure
- Regulatory approval in US (2014) and EU (2015)
  - In the US, 32% of all GD1 adult patients are treated with Cerdelga (~600 patients)
  - Cerdelga is currently approved in 28 countries.
  - Worldwide, approximately 1500 patients are being treated with Cerdelga





1.Cerdelga Summary of Product Characteristics Dec 2019. 2. Lukina E et al. *Blood*. 2010;116:893-899. 3. Mistry PK et al. *JAMA*. 2015;313(7):695-706. 4. Cox TM et al. *Lancet*. 2015;385(9985):2355-2362. 5. Charrow J et al. *Mol Gen Metab*. 2018;123:347-356. Sanofi data on file; Qlicksens Insights dashboard.

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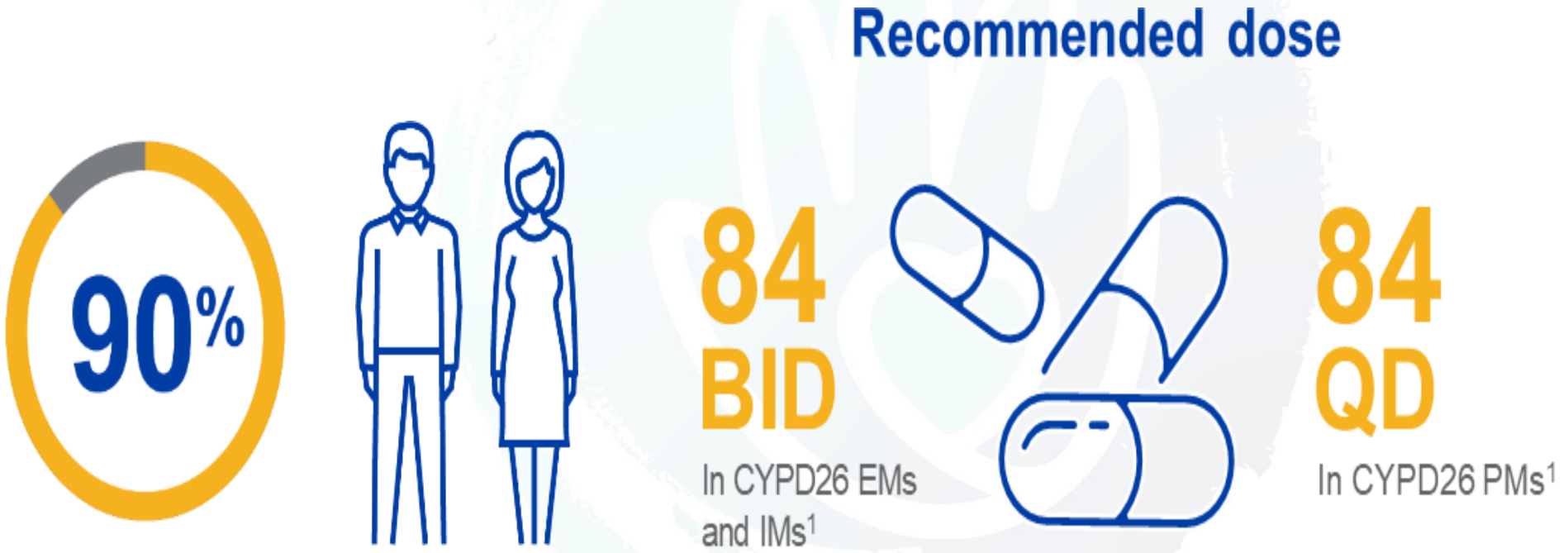
# Patient Eligibility Determined by User Metabolizer Status

Options

**Cerdelga is indicated for the long-term treatment of adult patients with GD1, who are CYP2D6 poor metabolizers (PMs), intermediate metabolizers (IMs) or extensive metabolizers (EMs)**

More than 90% of GD1 patients in Cerdelga clinical trials (N=393) were CYP2D6-metabolizer–compatible[1,2]




**Cerdelga Is Dosed BID or QD Depending on CYP2D6 Metabolizer Status**

In CYP2D6 EMs and IMs[1]

In CYP2D6 PMs[1]


1. Mistry PK et al. *Am J Hematol*. 2017;92(11):1170-1176.
2. Cerdelga Summary of Product Characteristics (SmPC) Genzyme Europe B.V. Jan 2020.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Options

GAUCHER REGISTRY

I C G G

HEMATOLOGIC • VISCERAL • SKELETAL • QUALITY OF LIFE

# Real-world effectiveness of eliglustat in treatment-naïve and switch patients enrolled in the International Collaborative Gaucher Group Gaucher Registry

Pramod Mistry, Manisha Balwani, Joel Charrow, Priya Kishnani, Claus Niederau, Lisa Underhill, Monica McClain

*American Journal of Hematology 2020*

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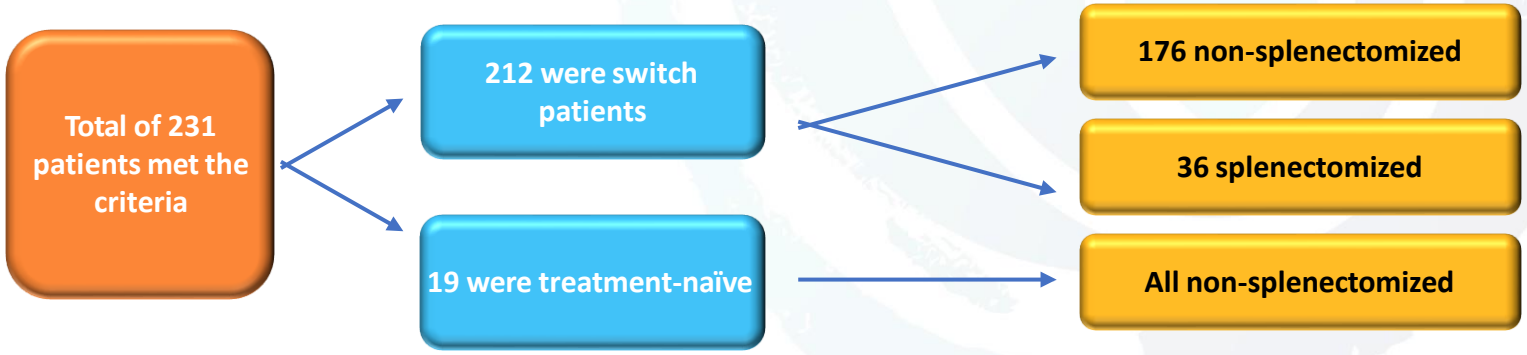
# 231 Cerdelga-treated Patients From the ICGG Gaucher Registry

Options

- Among 6341 patients enrolled in the ICGG Gaucher Registry as of January 2019, 466 had been treated with eliglustat.
- Among these eliglustat-treated patients, **231** met the following criteria and had:
  - Eliglustat treatment dates
  - Confirmed Gaucher disease Type 1 with a diagnosis date
  - Known splenectomy status (including date of splenectomy if splenectomized)
  - Been treated with eliglustat for at least **1 year**
  - Baseline and 2-year data (plus or minus 1 year) while on eliglustat and no other GD therapy for at least one key parameter: hemoglobin, platelet count, liver volume, spleen volume, bone pain or bone crisis




- 87% of patients had genotypes associated with less severe disease (at least one N370S allele).
- 96% of patients were eligible for eliglustat based on CYP2D6 metabolizer status.
- 89% of patients were from the United States, the first country to approve eliglustat

Mistry PK et al. *Am J Hematol.* 2020 May 21. doi: 10.1002/ajh.25875. Online ahead of print.

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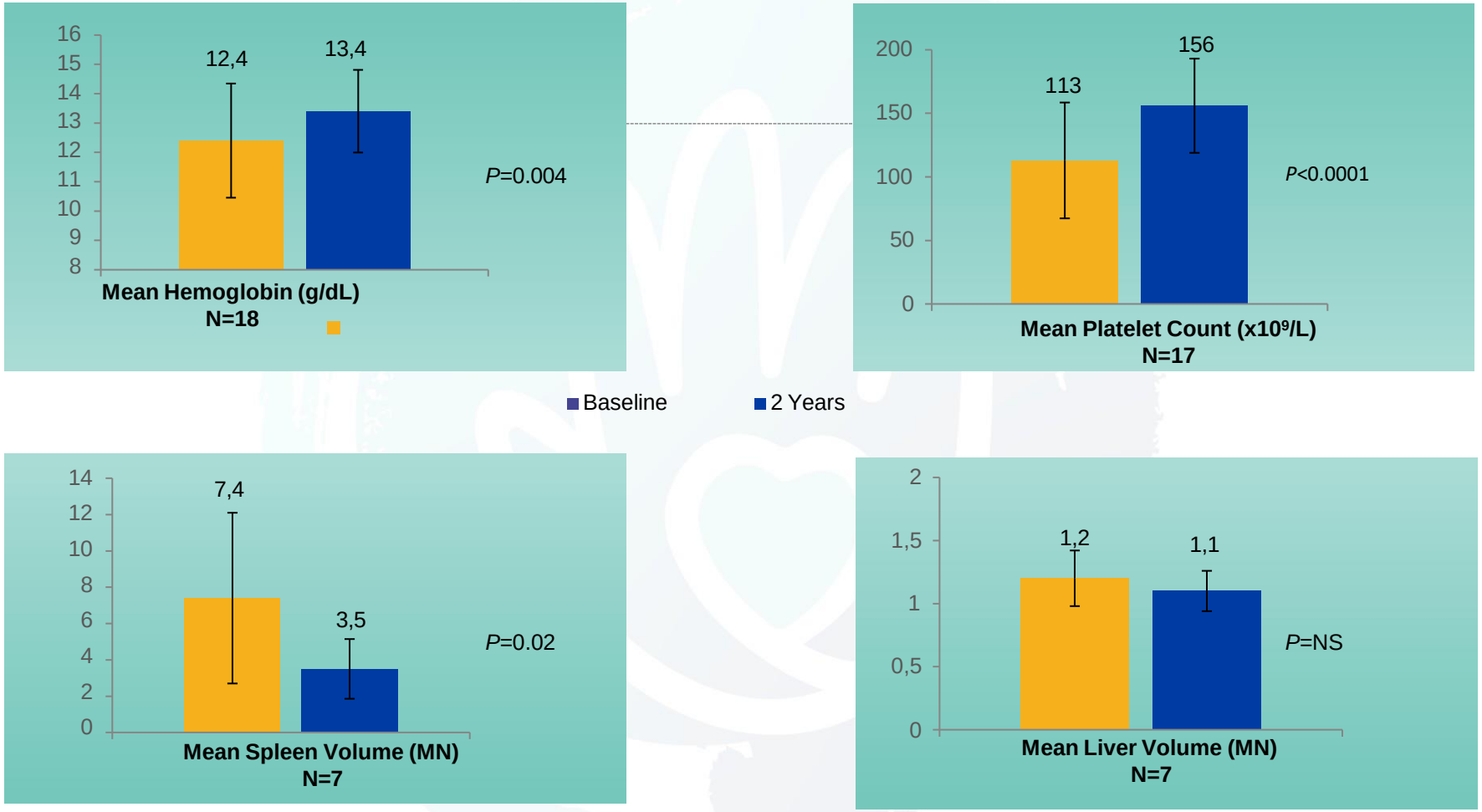
# Treatment-Naïve Patients Had Clinically and Statistically Significant Improvements in Hemoglobin, Platelets, and Spleen Volume After 2 Years on Cerdelga

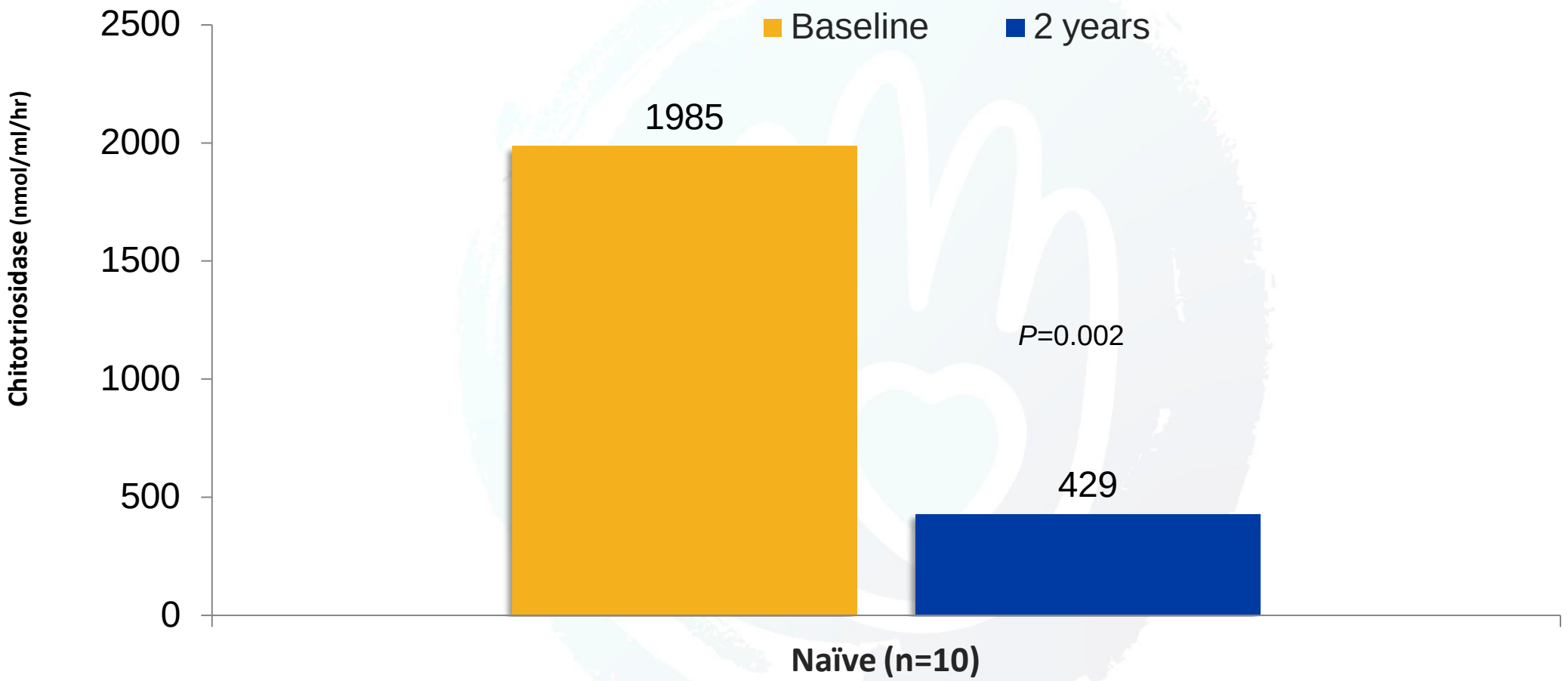



*P* values are from a paired t-test comparing 2-year parameters to baseline.

Mistry et al. *Am J Hematol.* 2020 May 21. doi: 10.1002/ajh.25875. Online ahead of print.

# Significant Decrease in Median Chitotriosidase in Treatment-Naïve Patients

Options




Baseline
Min, Max: 50, 8990

*P value is from the Signed Rank test (nonparametric), comparing 2-year values to baseline.

Mistry et al. *Am J Hematol.* 2020 May 21. doi: 10.1002/ajh.25875. Online ahead of print.

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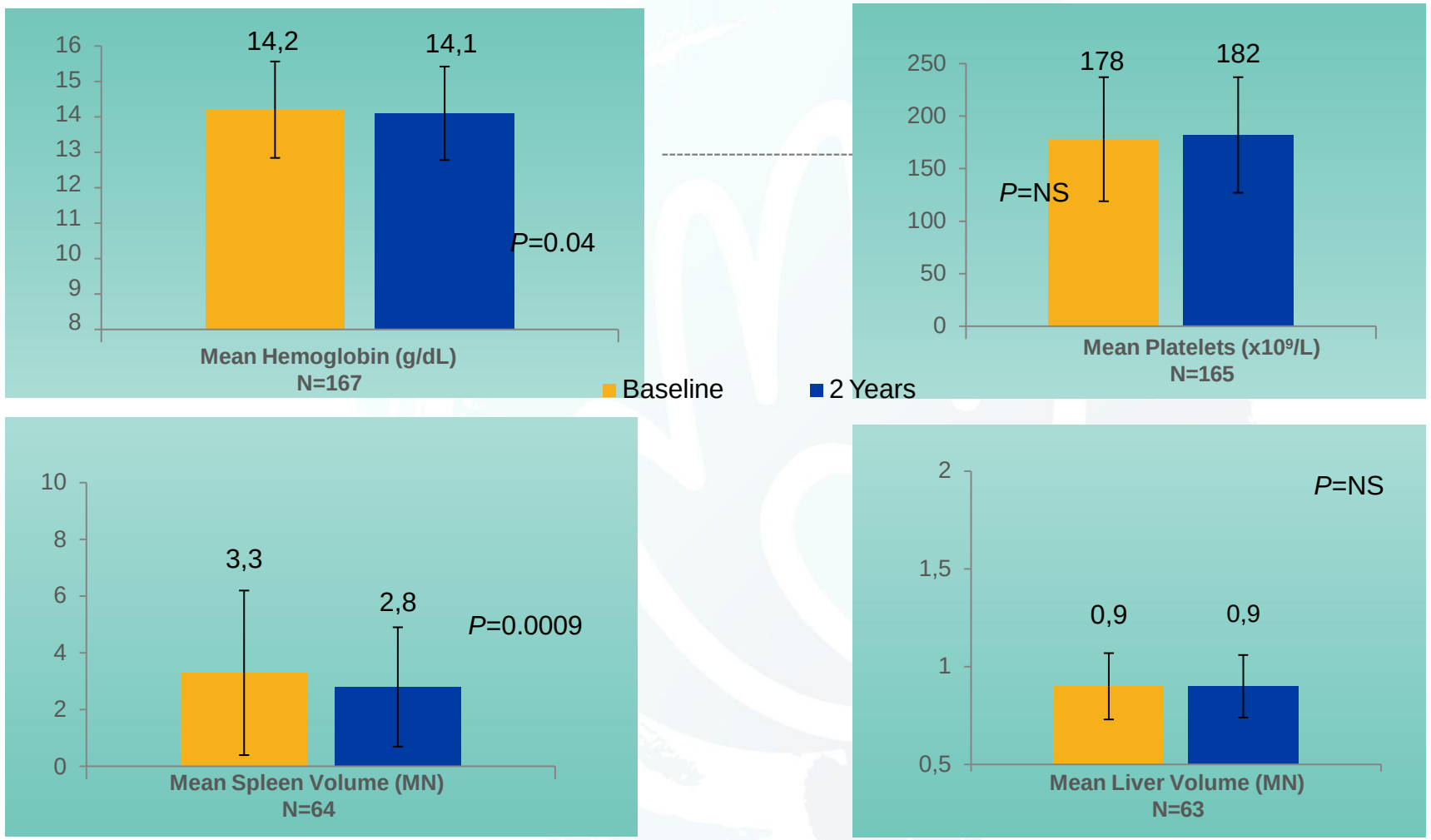
# Stability Maintained and Significant Reduction in Spleen Volume in Non-Splenectomized Switch Patients






Mistry et al. *Am J Hematol.* 2020 May 21. doi: 10.1002/ajh.25875. Online ahead of print.

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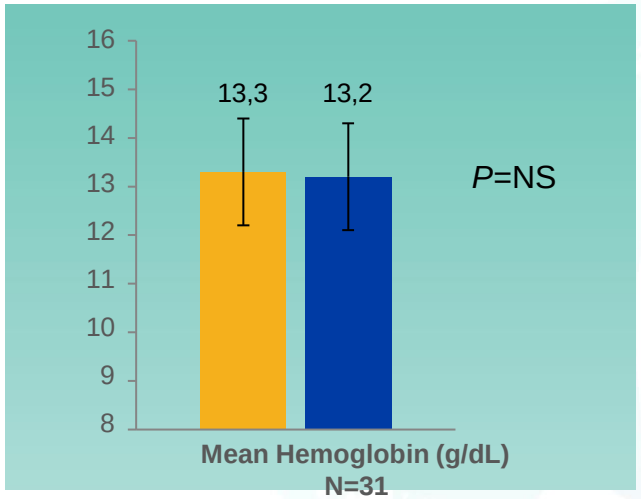
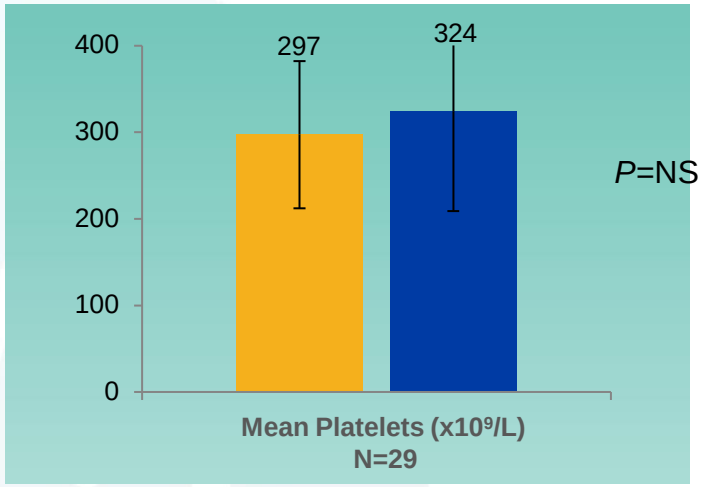
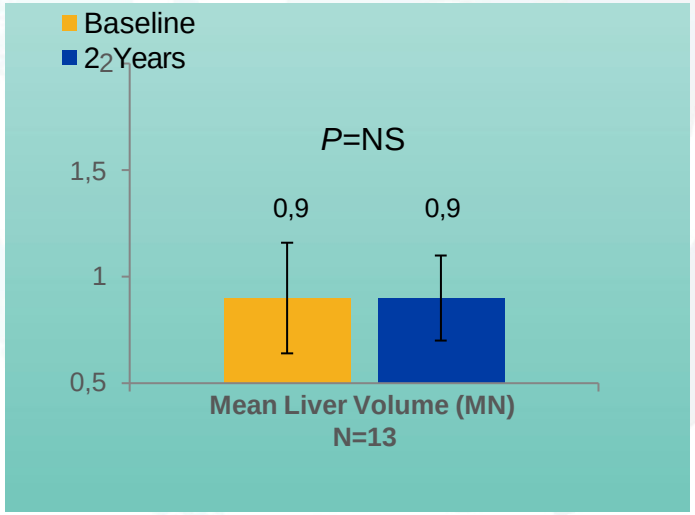
# Stability Maintained in Splenectomized Switch Patients With Cerdelga





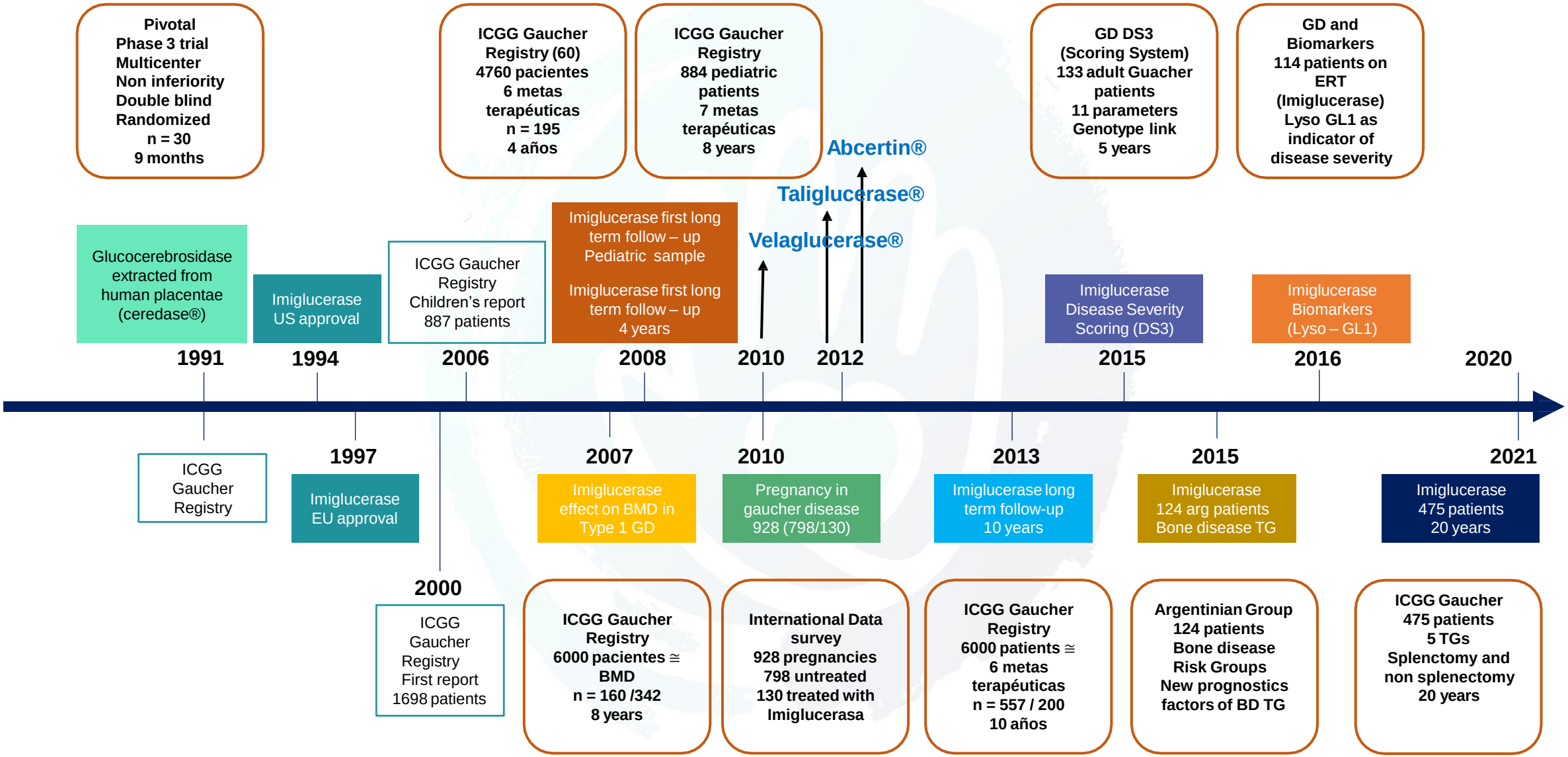

Mistry et al. *Am J Hematol.* 2020 May 21. doi: 10.1002/ajh.25875. Online ahead of print.

# Summary of Real-World Evidence from the ICGG Gaucher Registry

- Analysis of the ICGG Gaucher Registry provides real-world evidence of Cerdelga efficacy that is consistent with reports from the Phase 2 and Phase 3 clinical trials
- This analysis demonstrated long-term benefit of Cerdelga in treatment-naïve patients and ERT switch in patients, in keeping with established therapeutic goals for Gaucher disease type 1

Mistry et al. *Am J Hematol.* 2020 May 21. doi: 10.1002/ajh.25875. Online ahead of print.

# Safety and Efficacy in Gaucher Disease




22. Vagishwari Murugesan, Pramod K. Mistry et al. Glucosylsphingosine is a key biomarker of Gaucher disease. American Journal of Hematology, Vol. 91, No. 11, November 2016

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# Summary

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## Nicolás Fernández Escobar

- Información Doctor CV
- Estudios
- Trabajos de importancia

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# The Team

## GADTEG



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