Gaucher Disease

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Slides adapted from Manisha Balwani, MD, MS

Conflicts of Interest

- Honoraria for participation in advisory boards for PTC Therapeutics and BioMarin

Learning Objectives

- Understand the pathophysiology and key clinical features of Gaucher disease
- Identify key diagnostic tests and interpret results
- Explain the genotype-phenotype correlations
- Describe the indications for treatment and explain therapeutic options
- Understand addition risks, including malignancy, for patients with Gaucher disease

Outline

- Pathophysiology & Disease Overview
- Phenotypes/Clinical Presentation
- Diagnosis & Evaluation
- Treatment & Management
- Additional Considerations

Pathophysiology & Disease Overview

Gaucher Disease Background

- Autosomal recessive
- *GBA1* gene

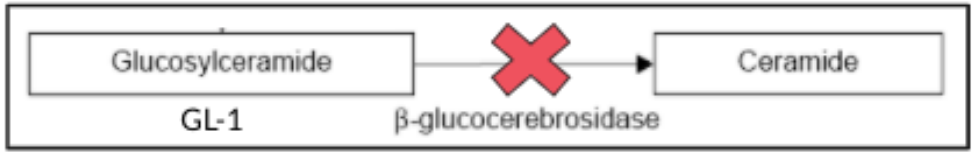
Deficiency of the lysosomal enzyme acid-β-glucosidase

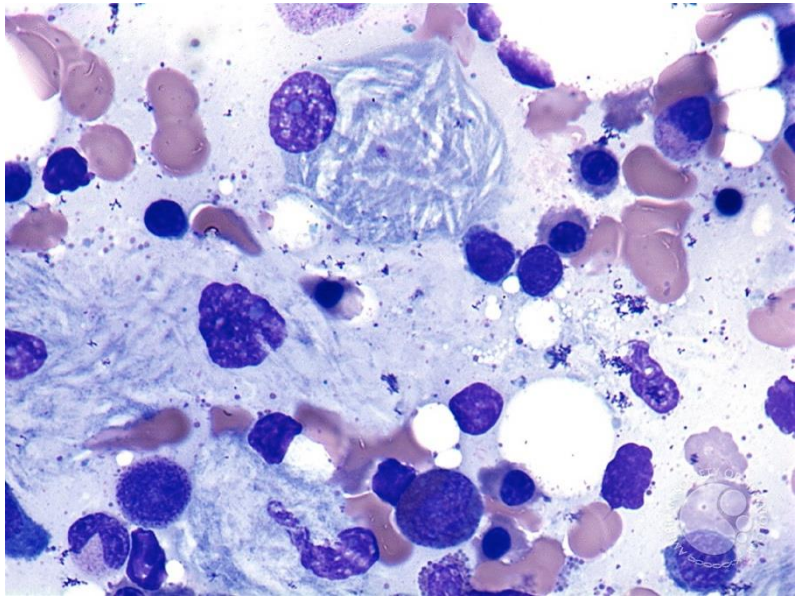
↓

Storage of glucosylceramide (GL-1) primarily in cells of the monocyte/macrophage lineage

↓

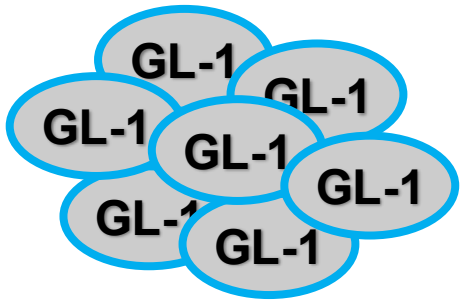
Progressive, multi-organ dysfunction primarily involving the reticuloendothelial system





Deficient GBA Leads to Lysosomal Accumulation of GL-1

GBA = glucosidase, beta acid = glucocerebrosidase
GL-1 = glucosylceramide = ceramide-glucoside = glucocerebroside



~~GBA~~ + H_2O

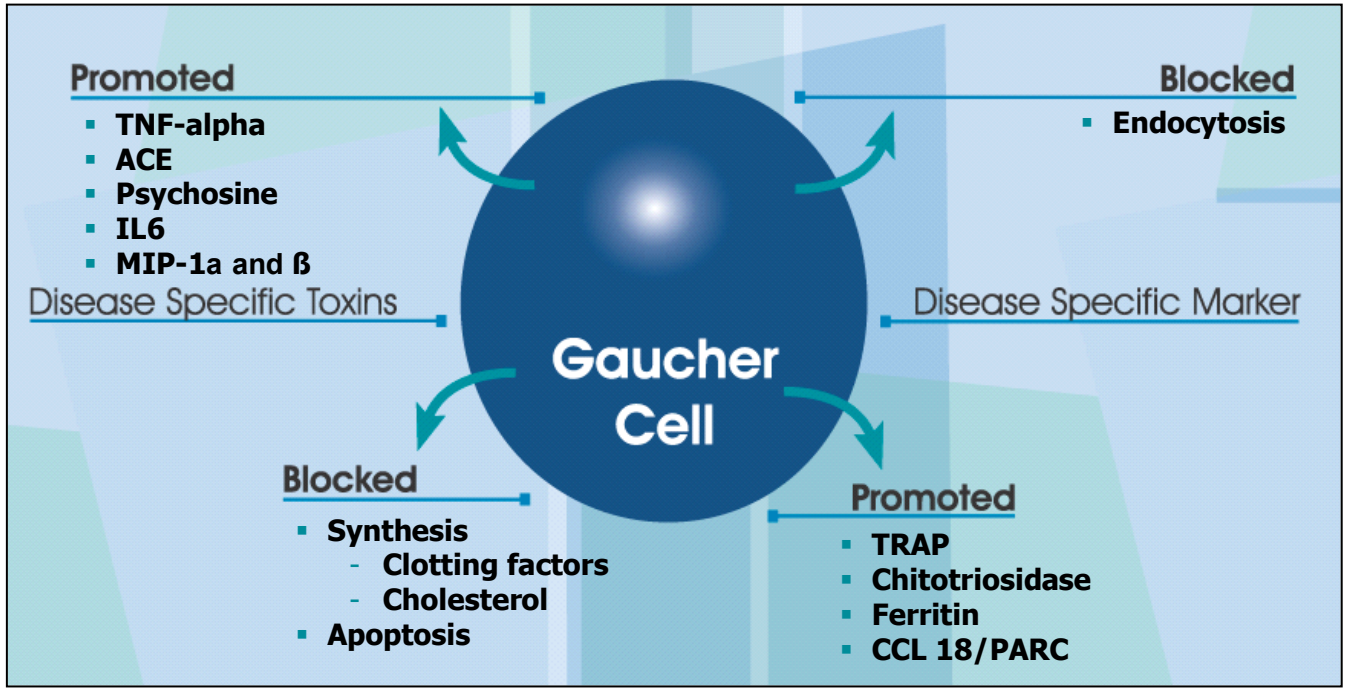
Saposin C +
Anionic Phospholipids

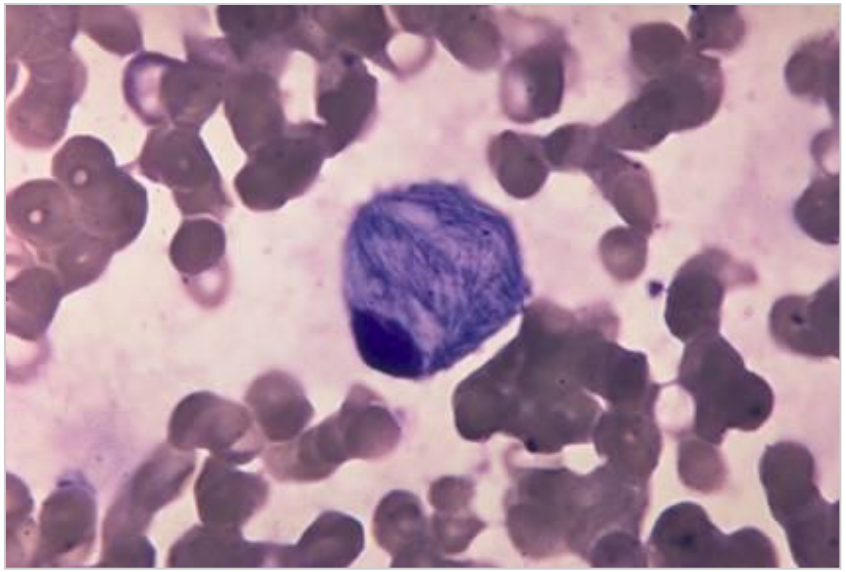
Ceramide + Glucose

Glucosylsphingosine

Gaucher Cells

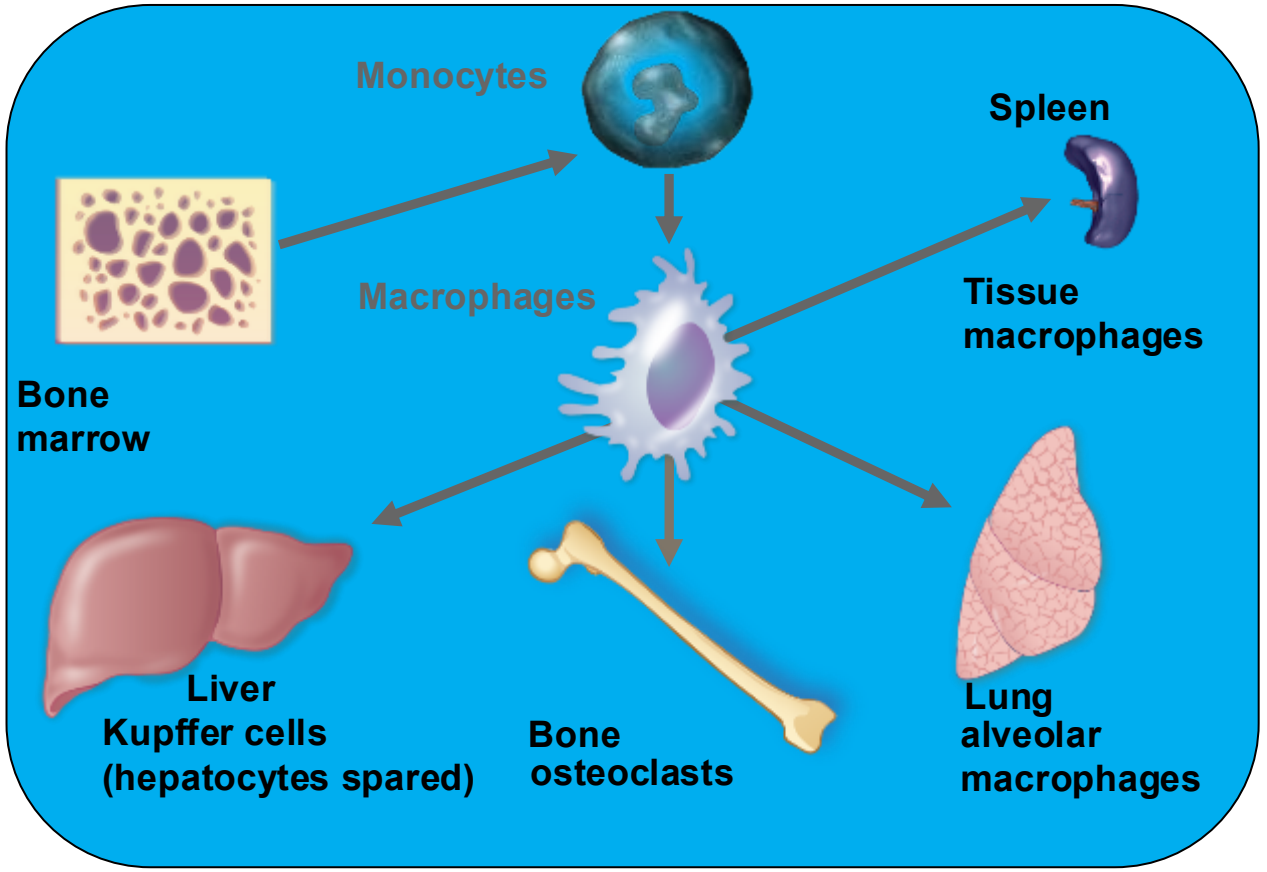
Gaucher cells filled with glycosphingolipids accumulate in the reticuloendothelial system





These cells release cytokines which can lead to organ damage

Pathophysiology



- Bone marrow infiltration
- Cytopenia

- Massive splenomegaly
- Cytopenia
- Hypermetabolic state: fatigue

- Hepatomegaly

- Infiltrative lung disease

- Avascular osteonecrosis
- Osteoporosis
- Pathological fractures
- Chronic bone pain

Grabowski et al. *OMMBID Online*. 2014.

Phenotypes/Clinical Presentation

GD Clinical Subtypes

Type 1

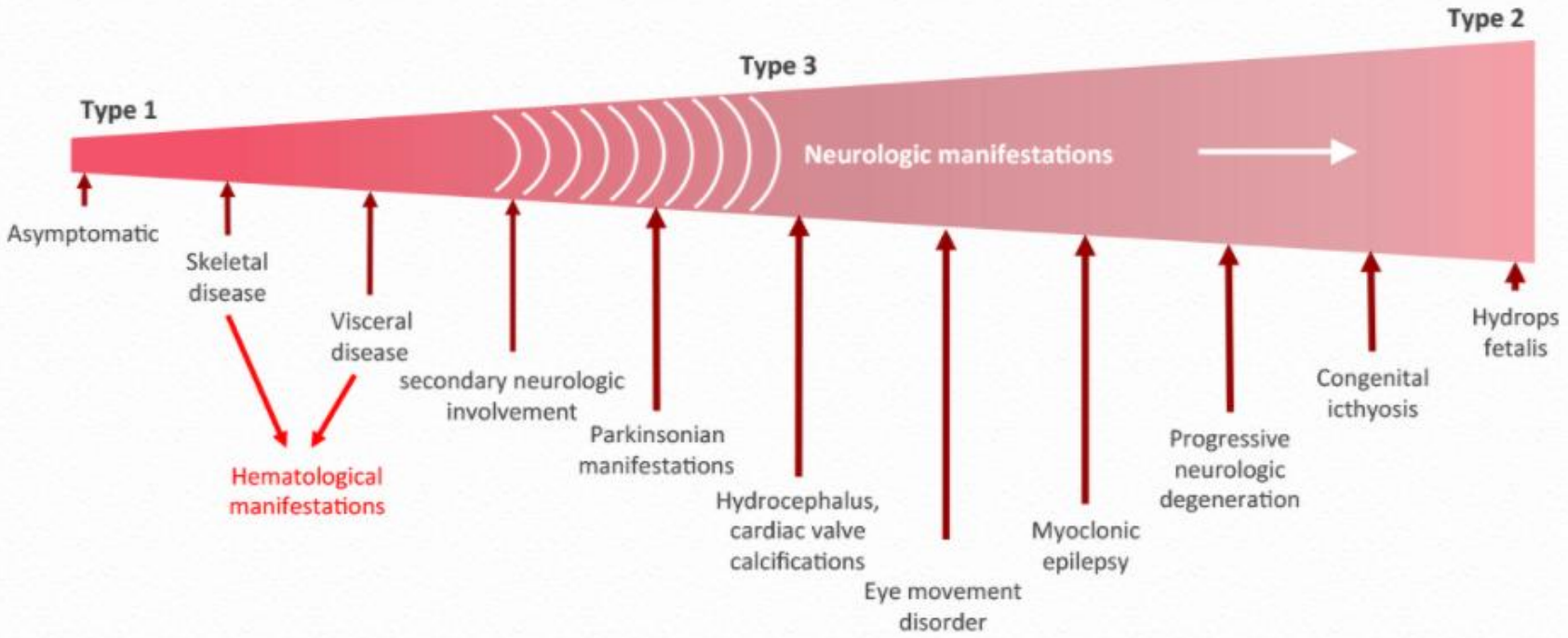
the most common form, and is non-neuronopathic, accounting for >90% of all Gaucher disease patients.[5]

Type 2

an acute neuronopathic form with early onset and a rapid, degenerative course that results in death usually within the first 2 years of life.

Type 3

a chronic neuronopathic form with a less rapid course and milder symptoms than Type 2 that results in death in childhood to early adulthood



1. SIDRANSKY, E. Mol Gen Met 2004; 83: 6–15.
2. GRABOWSKI, GA. Lancet 2008; 372: 1263–71
3. NAGRAL A. J Clin Exp Hepatol. 2014; 4:37–50.
4. HOPKIN RJ et al. (Chapter) Fauci AS et al. Harrison's Principles of Internal Medicine.
5. MISTRY, P. et al. Am J Hematol 2011; 86(1): 110–5.

GD Clinical Subtypes

Characteristic	Type I		Type II		Type III		
	Symptomatic	Asymptomatic	Infantile	Neonatal	IIIa	IIIb	IIIc
Most common genotype	*1226G* compound heterozygous	*1226G* (*N370S*) homozygous	None	Two null mutations	None	*1448C* (*L444P*) homozygous	*1342C* (*D409H*) homozygous
Ethnic predilection	Ashkenazi Jews	Ashkenazi Jews	None	None	None	Norbottnians (Northern Sweden)	Palestinian Arab Japanese
Common presenting features	Hepatospleno-megaly Hypersplenism Bleeding Bone Pains	None	OMA Strabismus Opisthotonus Trismus	Hydrops fetalis Congenital ichthyosis	OMA Myoclonic seizures	OMA Hepatospleno-megaly Growth retardation	Cardiac valve calcification
Central nervous system involvement	None	None	Severe	Lethal	Slow progressive neurological deterioration	OMA Slow cognitive deterioration	OMA
Bone involvement	Mild to severe	None	None	None	Mild	Moderate to severe	Small
Lung involvement	None to severe	None	Severe	Severe	Mild to moderate	Moderate to severe	Small
Enzyme replacement therapy	Indicated and efficient	Not indicated	Ethically problematic	Not relevant	Recommended for visceral features only		
Life expectancy	Normal	Normal	Death before age 2 years	Neonatal death	Death during childhood	Possible survival to adulthood	Survival to teenage

OMA=oculomotor apraxia.

Ref: OMMBID

Genotype/Phenotype Correlations

N370S/N370S	Type 1; Non-Neuronopathic Mild to Severe
N370S/L444P	Type 1: Non-Neuronopathic
N370S/IVS2^{+1} N370S/84GG	More Severe, Childhood Onset
L444P/L444P	Type 2 or 3: Severe Neuronopathic
D409H/D409H	Type 3: Neuronopathic; Cardiac involvement

Demographic Characteristics of All Patients Enrolled in the ICGG Gaucher Registry

	Statistic	Europe	JAPAC	Latin America	Middle East	North America	Global*
Total Patients**	N	1488	201	926	842	2335	5795
Gaucher Disease Type†	n	1464	198	917	816	2285	5683
Type 1	n (%)	1323 (90.4)	160 (80.8)	872 (95.1)	726 (89.0)	**2169 (94.9)**	5252 (92.4)
Type 2	n (%)	9 (0.6)	2 (1.0)	10 (1.1)	3 (0.4)	**33 (1.4)**	57 (1.0)
Type 3	n (%)	**132 (9.0)**	**36 (18.2)**	**35 (3.8)**	**87 (10.7)**	**83 (3.6)**	374 (6.6)
Sex	n	1488	201	926	842	2335	5795
Male	n (%)	674 (45.3)	107 (53.2)	379 (40.9)	420 (49.9)	1118 (47.9)	2699 (46.6)
Female	n (%)	814 (54.7)	94 (46.8)	547 (59.1)	422 (50.1)	1217 (52.1)	3096 (53.4)
Age at Gaucher Diagnosis (years)	n	1434	187	894	789	2216	5521
	Mean (SD)	**20.9 (17.46)**	**9.8 (11.58)**	**16.5 (14.89)**	**18.2 (18.75)**	**22.4 (19.70)**	20.0 (18.27)
	Median (25th,75th)	16.3 (5.8, 32.3)	5.0 (2.0, 12.7)	10.8 (5.1, 24.6)	12.0 (3.1, 27.4)	18.2 (5.1, 34.6)	14.2 (4.9, 30.9)
	Min, Max	-0.3, 80.0	0.0, 59.6	-0.9, 80.2	-0.5, 76.7	-0.7, 91.1	-0.9, 91.1
Primary Gaucher Therapy Status	n	1488	201	926	842	2335	5795
Never Treated	n (%)	181 (12.2)	6 (3.0)	81 (8.7)	443 (52.6)	457 (19.6)	1170 (20.2)
Imiglucerase-Treated	n (%)	1307 (87.8)	195 (97.0)	845 (91.3)	399 (47.4)	1878 (80.4)	4625 (79.8)

Min: minimum, Max: maximum, SD: standard deviation

* Global data includes patients from Europe, JAPAC, Latin America, Middle East, and North America regions; and New Zealand

** "Total Patients" (N) includes all patients with all disease types who met inclusion criteria for analysis. Subsequent counts (n) indicate numbers of patients for whom data were available.

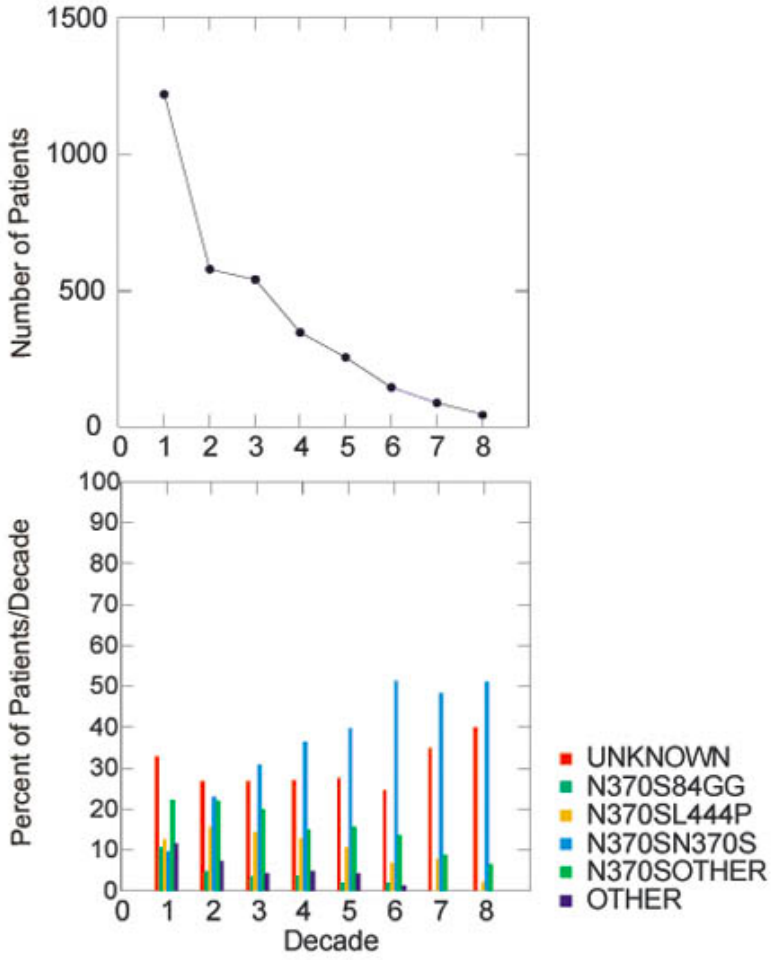
† Disease type reported by physician.

ICGG: International Collaborative Gaucher Group

Type 1: Non-neuronopathic Gaucher Disease

- Non-neuronopathic GD is the most prevalent form
  - Accounts for 94% of cases
- Differentiated by the other forms by lack of primary central nervous system involvement
- Clinical expression is highly variable
- When manifest in childhood, it can be a progressive, multisystemic and debilitating disorder

Type 1 GD: Age at Presentation

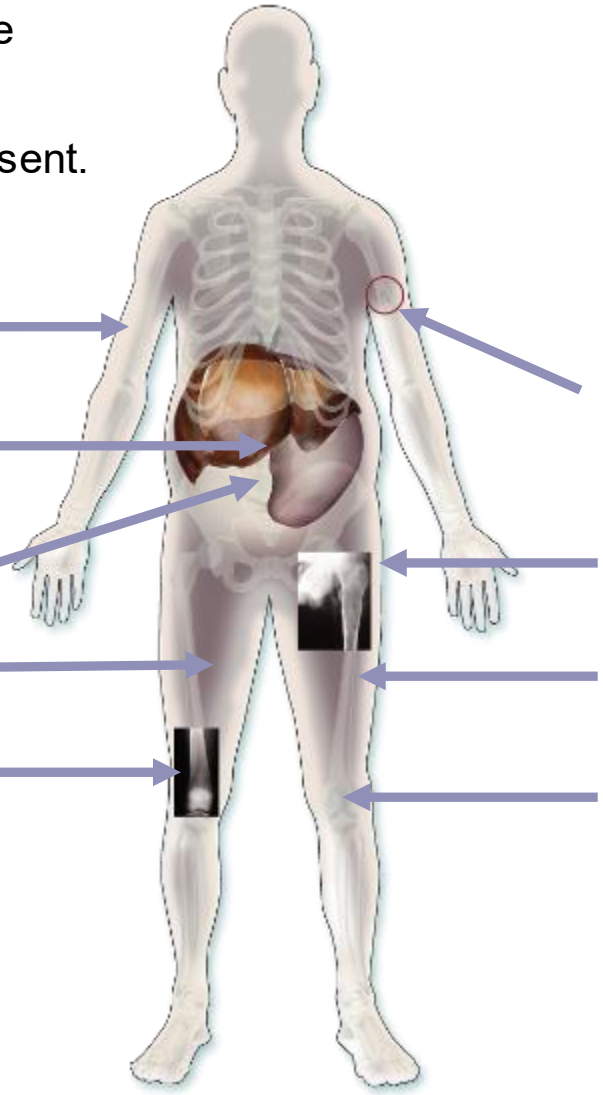


From: Gaucher Disease: Phenotypic and Genetic Variation
The Online Metabolic and Molecular Bases of Inherited Disease, 2019

Type 1 GD: A Multisystemic Disorder

Patients with GD1 can present with any of these symptoms.

Some may be severe and others completely absent.



Bone pain (63%)
Bone crisis (33%)

Hepatomegaly (79%)
Splenomegaly (87%)

Anemia (64%)
Thrombocytopenia (56%)

Erlenmeyer flask deformity (46%)

General symptoms:

- Fatigue
- Easy bruising/bleeding
- Menorrhagia
- Decreased appetite
- Abdominal pain

Pathologic fracture (15%)

Joint collapse (8%)

Osteonecrosis (25%)
Osteopenia (42%)

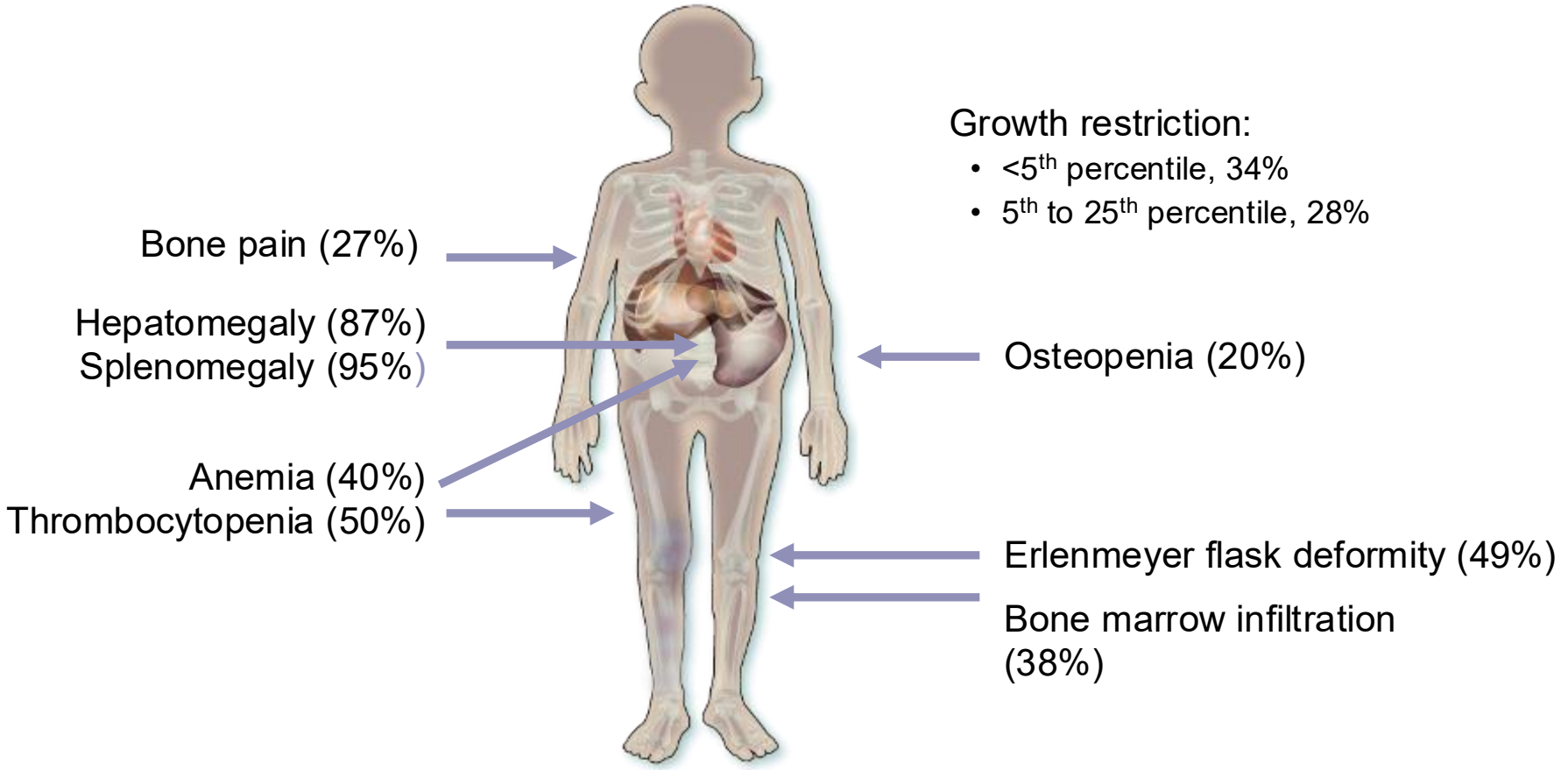
Bone marrow infiltration (40%)

Charrow et al. *Arch Intern Med*. 2000;160:2835.

GD1=Gaucher disease type 1.

Type 1 GD: Pediatric Presentation

- Children or adolescents with GD1 often have marked splenomegaly, easy bruising/bleeding/hypermenorrhagia and slower than normal growth and pubertal development.



Kaplan et al. *Arch Pediatr Adolesc Med*. 2006;160:603.

GD1=Gaucher disease type 1.

Diagnosis & Evaluation

How do patients come to medical attention?

- Patient has signs and symptoms (i.e splenomegaly, thrombocytopenia)
- Family studies (i.e sibling with the disease)
- Parents were found to be carriers (screening programs) and patient was tested at birth or after
- Newborn screening
  - LSD pilot NBS. Screening for GD and other LSDs
- Picked up through research or clinical studies for PD
- Incidental findings on exome or prenatal carrier screening

Type 1 GD Findings and Work-Up

Diagnosis

- Glucocerebrosidase activity assay
  - **Gold Standard for Dx**
- *GBA1* gene testing/mutation analysis (targeted mutation analysis or sequencing)
  - Pseudogene!
- Bone marrow biopsy (Gaucher cells)

Additional Work-Up

- MRI - b/l femurs, abdomen (volumetric)
- DEXA bone density scan

Laboratory Studies

- Chitotriosidase/Lyso-GL1
- CBC
- PT/PTT/INR
- Serum protein electrophoresis
- Serum immunofixation
- Vitamin D
- Ferritin

Biomarkers of Gaucher disease

Interpreted in conjunction with clinical assessments

Consistent, serial monitoring of one or more

Chitotriosidase

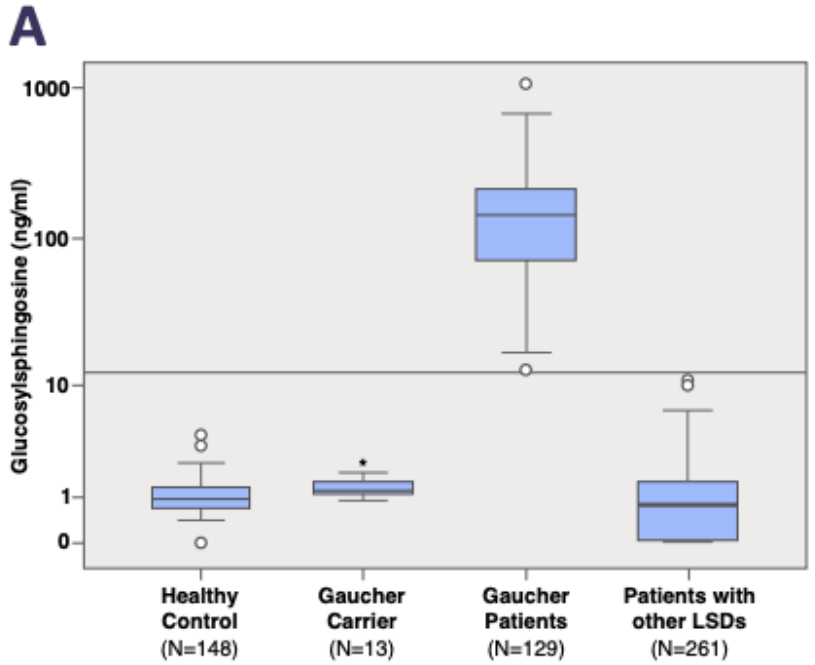
- Secreted by active macrophages
- Activity absent in some (6%) of patients (*CHIT1* genotype affects interpretation)
- Serial increases may be early indicator of clinical relapse
- Decreased activity with ERT

Lyso GL-1

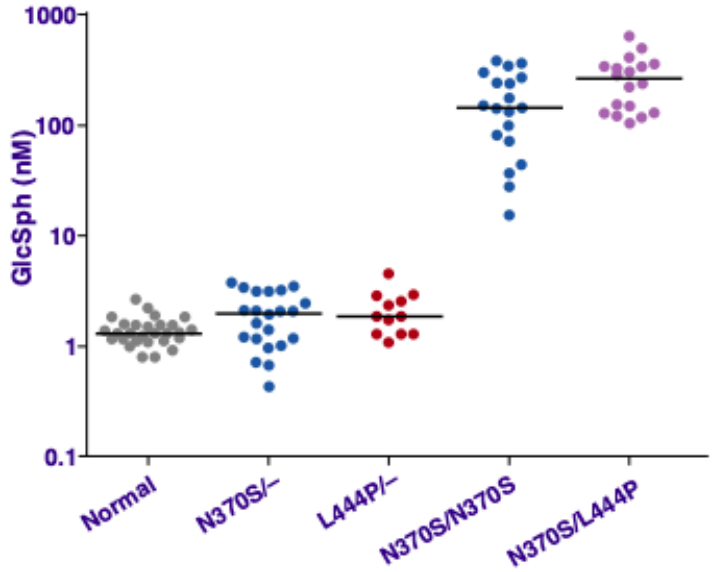
- May have greater utility with interpreting residual GD activity

Lyso-GL1

- Deacylated lysolipid, glucosylsphingosine (lyso-GL1)
- Key biomarker of GD
  - More recent studies reported elevated lyso-GL1 levels in tissues of GD1 patients compared to healthy controls and GD carriers
  - Differentiation by phenotype
- ERT reported to reduce lyso-GL1 levels



Adapted from: Rolfs A, et al. *PLoS One*. 2013;8(11):e79732.

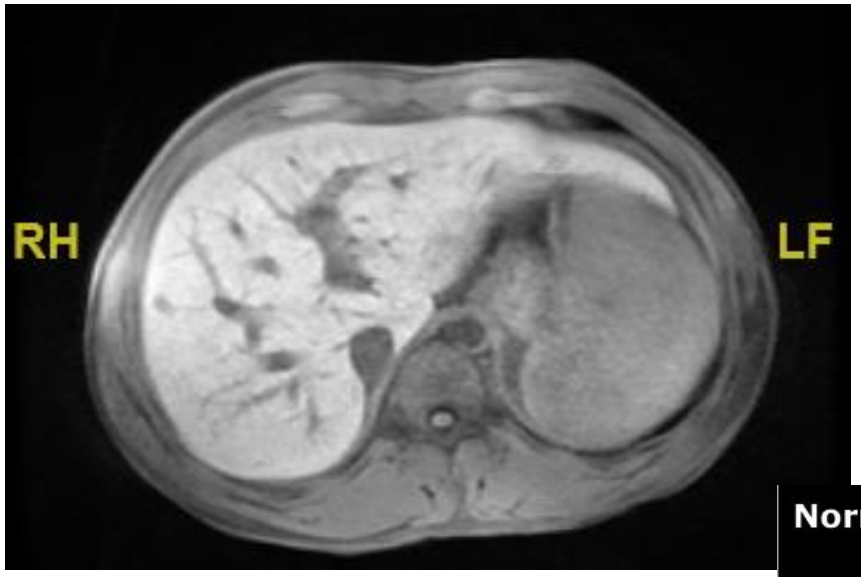


Adapted from: Dekker N, et al. Blood. 2011;118(16):e118-27.

Other Lab Findings

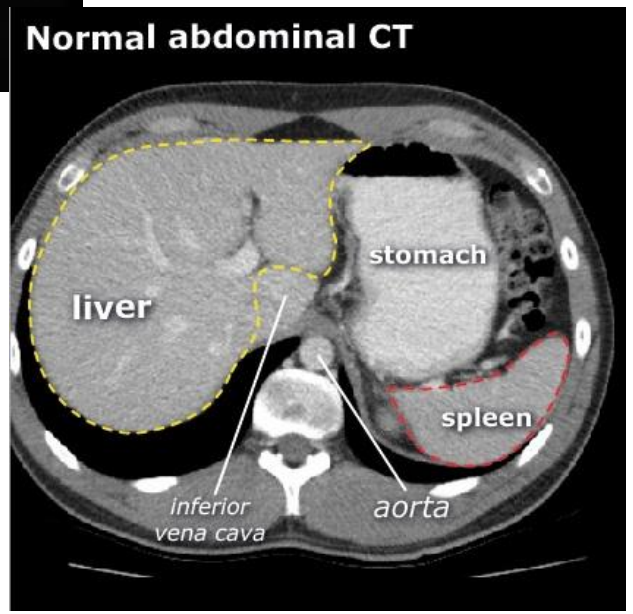
- Anemia
- Thrombocytopenia
- Elevated PT/PTT
- Elevated ferritin
- Low HDL/LDL
- Monoclonal or polyclonal gammopathy

Visceral



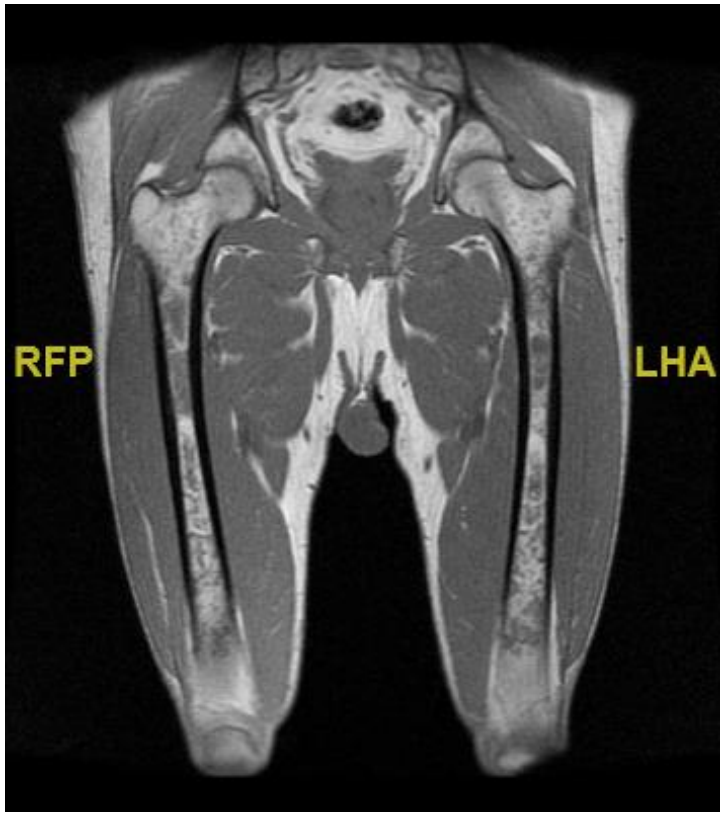
Hepatosplenomegaly seen on MRI of liver and spleen

- Increased Spleen and Liver volume
- Gaucher lesions in the liver/spleen
  - Small collections of Gaucher cells
- Iron deposition in the liver/spleen
- Gallstones



Gaucher Disease-Related Bone Disease

- At least 90% of Gaucher type 1 patients have evidence of bone disease at diagnosis.[1]
- Bone disease is the primary cause of morbidity and reduced quality of life for Gaucher patients.[2]
- Gaucher disease affects both bone marrow and cortical bone.
  - MRI reveals “dark marrow” caused by Gaucher cell infiltration
  - DXA reveals low bone mineral density
- This pathology can result in irreversible skeletal complications such as osteonecrosis, joint collapse, and pathologic fractures.

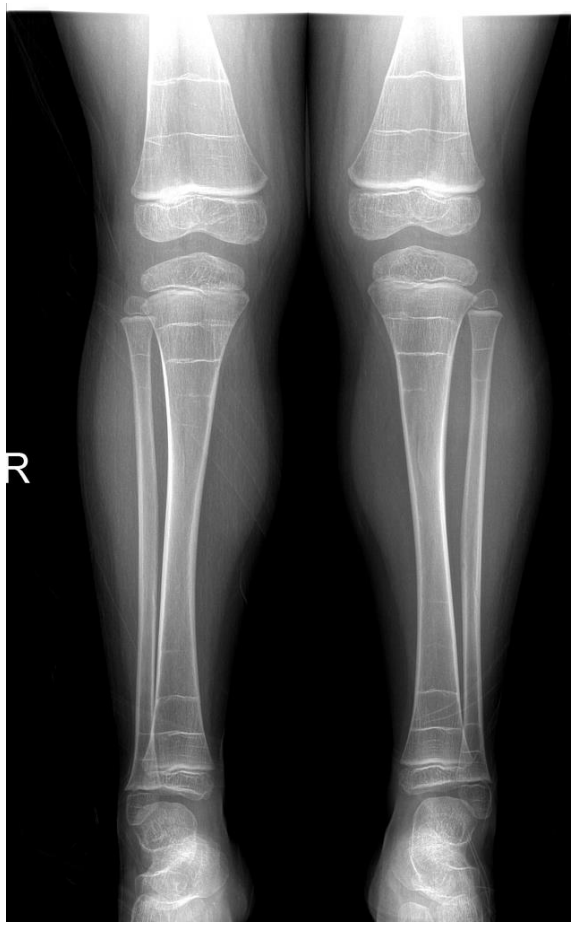


Diffuse infiltration, localized infarction of the R-proximal tibia

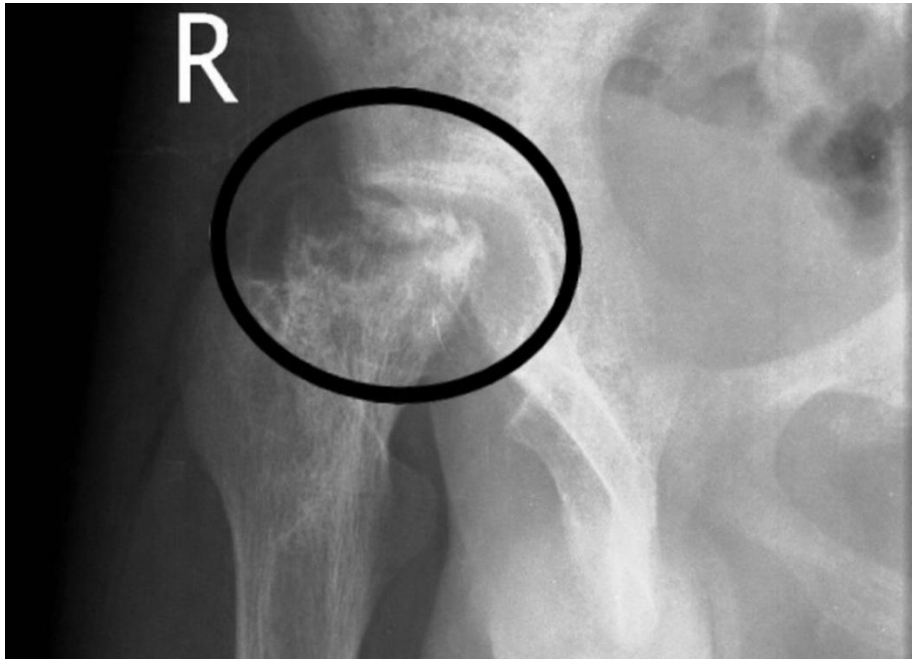
MRI=magnetic resonance imaging;
DXA=dual-energy X-ray absorptiometry

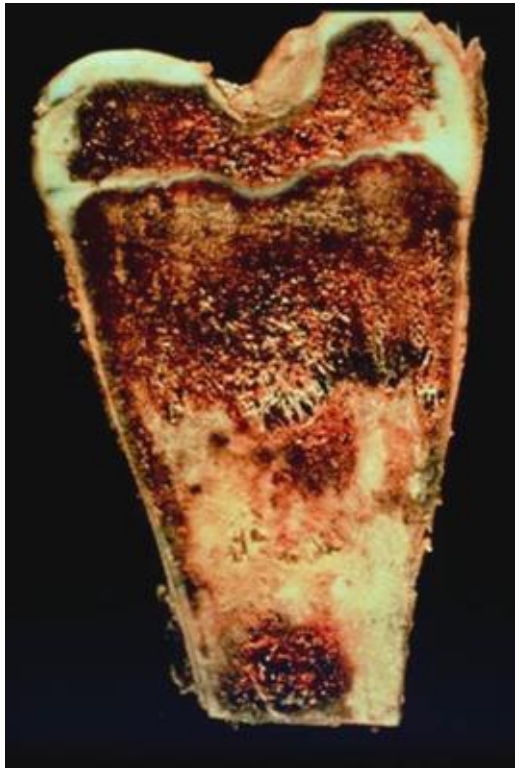
1. Charrow et al. *Arch Intern Med*. 2000;160:2835. 2. Weinreb et al. *Clin Genet*. 2007;71:576.

Erlenmeyer Flask Deformity and Osteosclerosis



Osteonecrosis





Gaucher Disease is a Chronic Heterogeneous Disorder

- Heterogeneity between patients
  - Different genotype
  - Same genotype

- Heterogeneity within the same patient
  - Severity among affected organ systems
  - Rate of progression or response to treatment among disease compartments

- Heterogeneous diseases cannot be managed in a homogeneous manner

- A patient-centered approach is needed for individualizing therapy

Treatment & Management

Indications for Treatment

- Anemia
- Thrombocytopenia
- Splenomegaly
- Bone disease

Initial dosing

- Objective: achievement of therapeutic goals based on
  - Age
  - Comprehensive initial assessment
  - Overall severity and progression of disease

Maintenance dosing

- Objective: maintenance of therapeutic goals based on results of regular, comprehensive monitoring

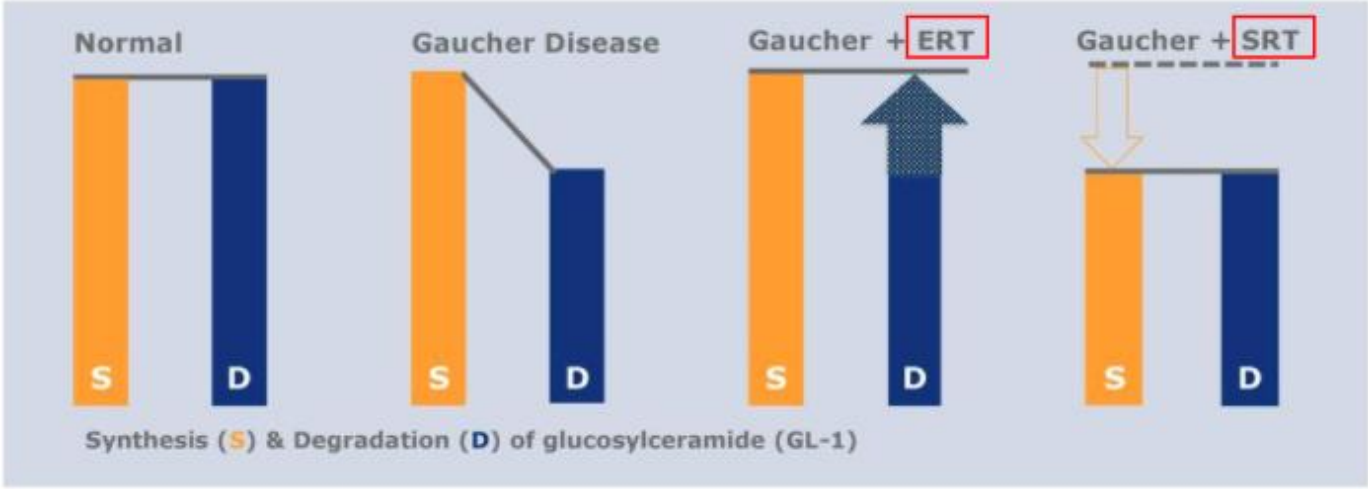
Gaucher Disease Treatment
Two Approaches: ERT and Substrate Reduction

Option One - Enzyme Replacement Therapy

- The gold standard (available since 1991)
- With Mannose-6-P for lysosomal targeting

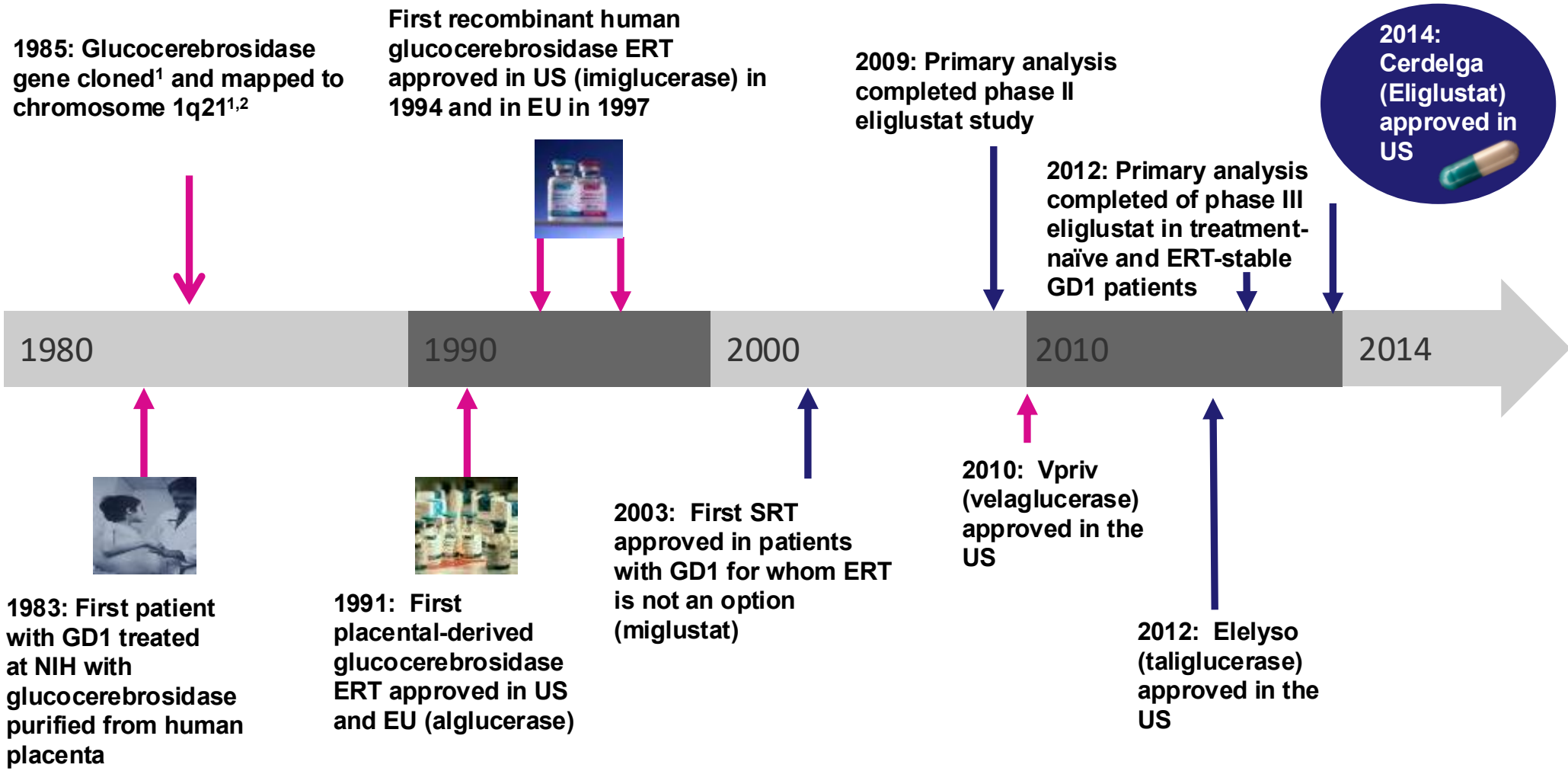
Option Two - Substrate Reduction Therapy

- Benefit of daily oral versus biweekly infusions
- CYP2D6 metabolizer status for eligibility
- Avoid drug interactions
- Exclusions for: pregnant or breastfeeding women, history of cardiac or kidney disease, history of hepatic impairment



For graphic illustration purposes only.
ERT=enzyme replacement therapy; SRT=substrate reduction therapy.
Shayman. *Drugs Future*. 2010:35:613.

Gaucher Disease Treatment Milestones



1. Sorge et al. *PNAS*.1985:82:7289. 2. Ginns et al. *PNAS* 1985;82:7101.

GD1=Gaucher disease type 1; IND=Investigational New Drug;
ERT= enzyme replacement therapy; SRT=substrate reduction therapy

Table 2. Comparison of FDA-approved enzyme replacement therapies[15,23-26]

	Imiglucerase (*Cerezyme*)	Velaglucerase alfa (*Vpriv*)	Taliglucerase alfa (*Elelyso*)
FDA approval	May 1994	February 2010	May 2012
FDA indication	Long-term enzyme replacement therapy for pediatric and adult patients with a confirmed diagnosis of type 1 Gaucher disease that results in one or more of the following conditions: anemia, bone disease, hepatomegaly or splenomegaly, thrombocytopenia	Long-enzyme replacement therapy for patients with type 1 Gaucher disease	Long-term enzyme replacement therapy for adult and pediatric patients with a confirmed diagnosis of type 1 Gaucher disease
Source	Recombinant DNA technology in Chinese hamster cell ovaries	Recombinant DNA technology in human fibroblast cells	Recombinant DNA technology in genetically modified carrot cells
Dosing	2.5 units/kg 3 times a week to 60 units/kg once every 2 weeks	• Starting dose of 60 units/kg every 2 weeks and titrate to effect • If switching from stable imiglucerase, start at same dose and begin velaglucerase alfa 2 weeks after the last imiglucerase dose	• Starting dose of 60 units/kg every 2 weeks • If switching from stable imiglucerase, start at same dose and begin taliglucerase alfa 2 weeks after the last imiglucerase dose
Administration	• Intravenous infusion administered over 1 to 2 hours • May be administered through an in-line low-protein-binding filter if flocculation occurs.	• Intravenous infusion administered over 1 hour • Administer through an in-line low protein-binding filter.	• Intravenous infusion over 1 to 2 hours • Administer through an in-line low protein-binding filter. • Pretreatment with antihistamines or corticosteroids may prevent infusion reactions.

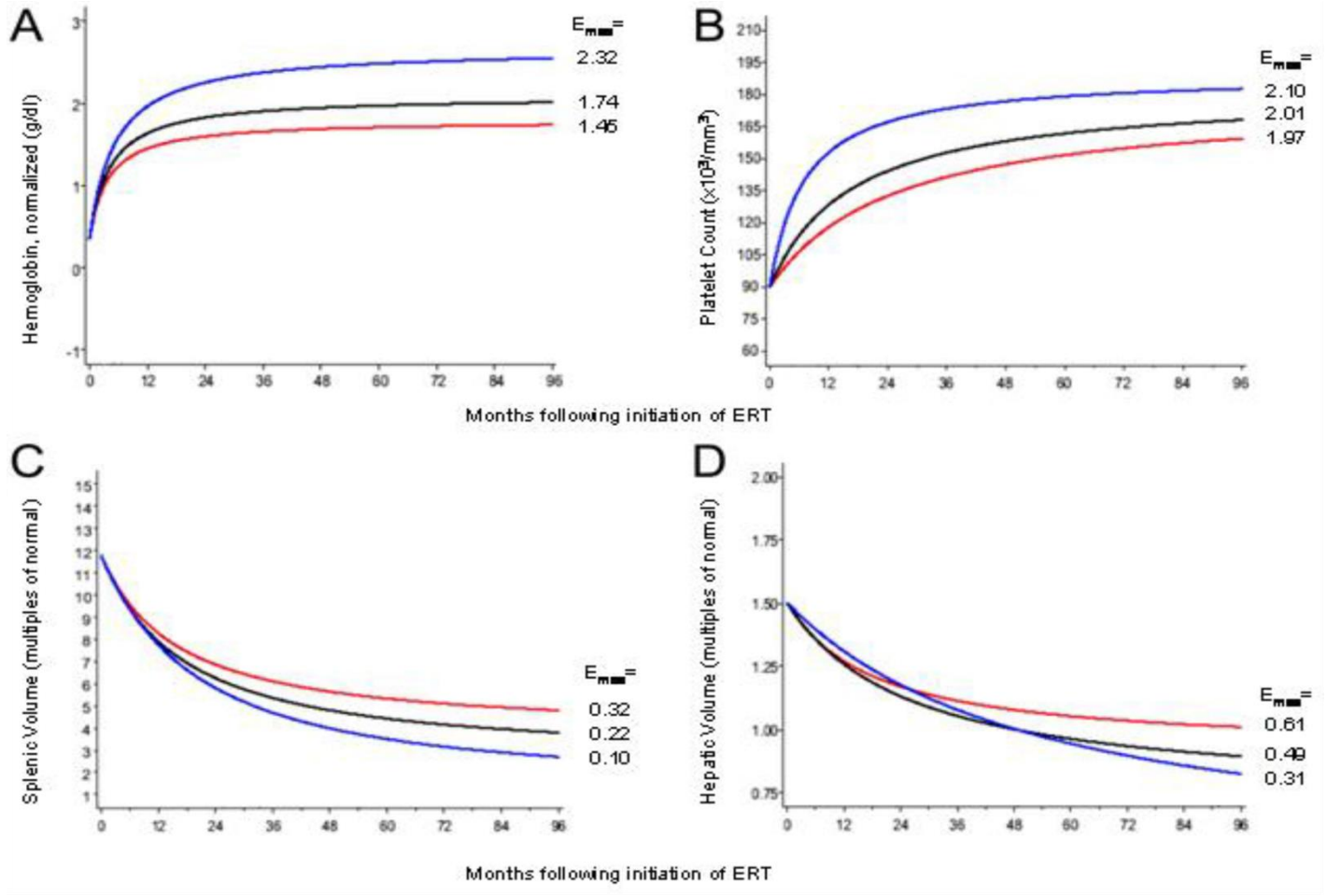
Van Rossum A, Holsopple M. Enzyme Replacement or Substrate Reduction? A Review of Gaucher Disease Treatment Options. Hospital Pharmacy. 2016 Jul;51(7):553-563. DOI: 10.1310/hpj5107-553.

Table 2. Comparison of FDA-approved enzyme replacement therapies[15,23-26] (CONT.)

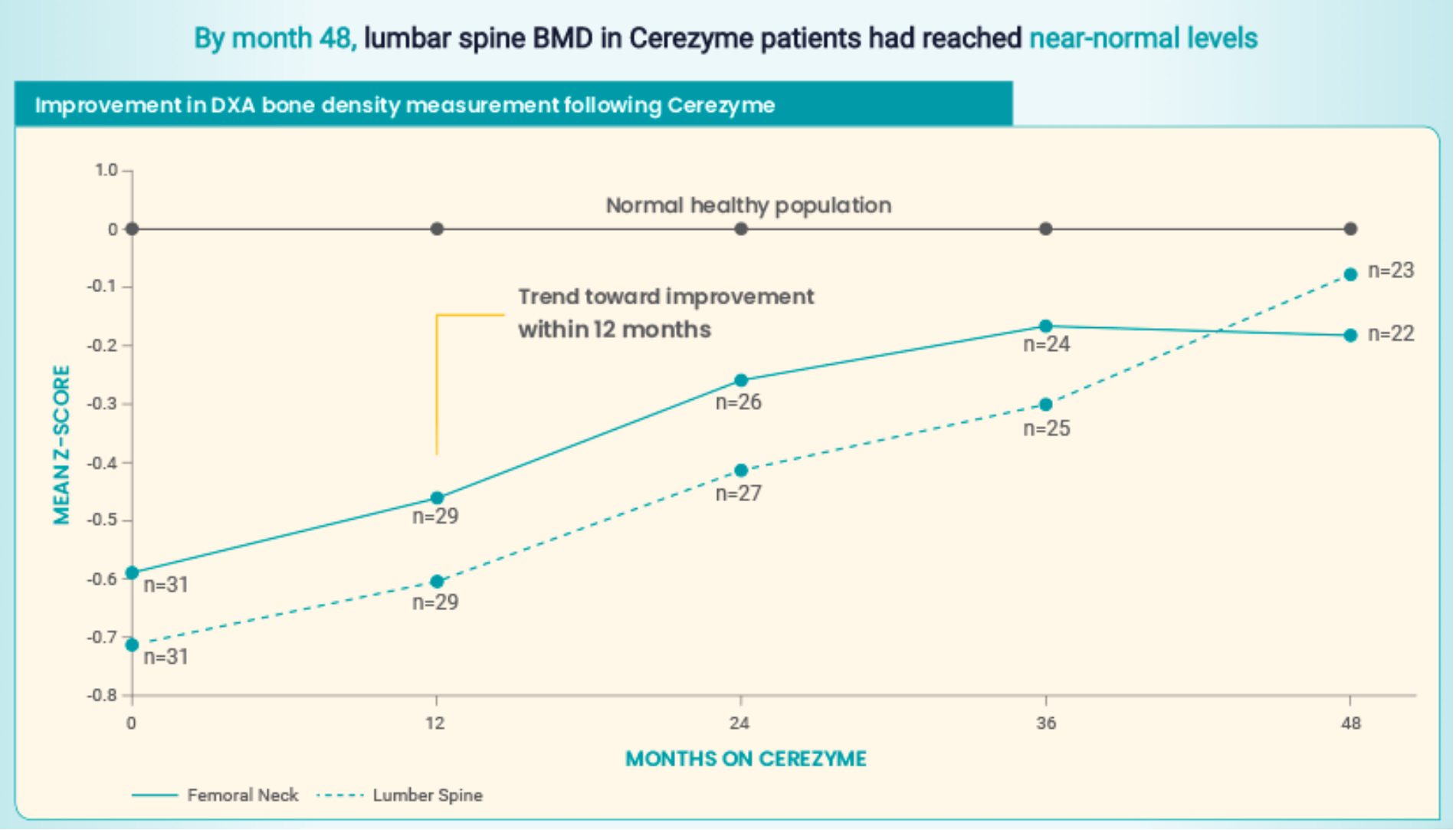
	Imiglucerase (*Cerezyme*)	Velaglucerase alfa (*Vpriv*)	Taliglucerase alfa (*Elelyso*)
Warnings	• Approximately 15% of patients develop IgG antibodies to imiglucerase in the first year of treatment. Patients must be monitored for IgG antibody formation during the first year of treatment. • Patients with detectable antibodies may experience hypersensitivity symptoms. • <1% of patients develop anaphylactic reactions. Most of these patients can continue imiglucerase therapy with pretreatment antihistamines or corticosteroids.	• Hypersensitivity reactions including anaphylaxis have occurred. • Hypersensitivity reactions may be managed by slowing the infusion rate or treatment with antihistamines or corticosteroids. • Pretreatment with antihistamines or corticosteroids may prevent subsequent reactions.	• Hypersensitivity reactions including anaphylaxis have occurred. • Hypersensitivity reactions may be managed by slowing the infusion rate, administering antipyretics, or antihistamines or corticosteroids. • Pretreatment with antihistamines or corticosteroids may prevent subsequent reactions.
Common adverse effects	Angioedema (<1.5%), chest discomfort (<1.5%), couching (<1.5%), cyanosis (<1.5%), dyspnea (<1.5%), flushing (<1.5%), hypotension (<1.5%), pruritus (<1.5%), urticaria (<1.5%)	Hypersensitivity (52%), headache (35%), dizziness (22%), pyrexia (22%), abdominal pain (19%)	Headache (19%), arthralgia (13%), fatigue (9%), nausea (9%), dizziness (9%)
Interactions	No known significant interactions	No known significant interactions	No known significant interactions
Pregnancy Category	• Pregnancy Category C • Animal reproductive studies have not been conducted and it is unknown if imiglucerase can cause fetal harm.	• Pregnancy Category B • Limited evidence in humans and no well-controlled studies conducted in pregnant humans. • No fetal harm was observed in rat or rabbit reproductive studies.	• Limited evidence in humans, which is insufficient to establish drug-associated risk in pregnant humans. • No fetal harm was observed in rat or rabbit reproductive studies.

Van Rossum A, Holsopple M. Enzyme Replacement or Substrate Reduction? A Review of Gaucher Disease Treatment Options. Hospital Pharmacy. 2016 Jul;51(7):553-563. DOI: 10.1310/hpj5107-553.

Effect of ERT treatment



Improved Bone Density with Long-term use of ERT



Treatment Goals

- Normalization of hemoglobin levels
- Improved platelet counts to safe levels
- Reduction of organ volumes
- Prevention of the need for splenectomy
- Prevention of bone crises and subsequent fractures
- Improvement in quality of life

Baldellou et al 2004

Substrate Reduction Therapy

Zavesca - Miglustat (*n*-butyl-deoxynojirimycin)

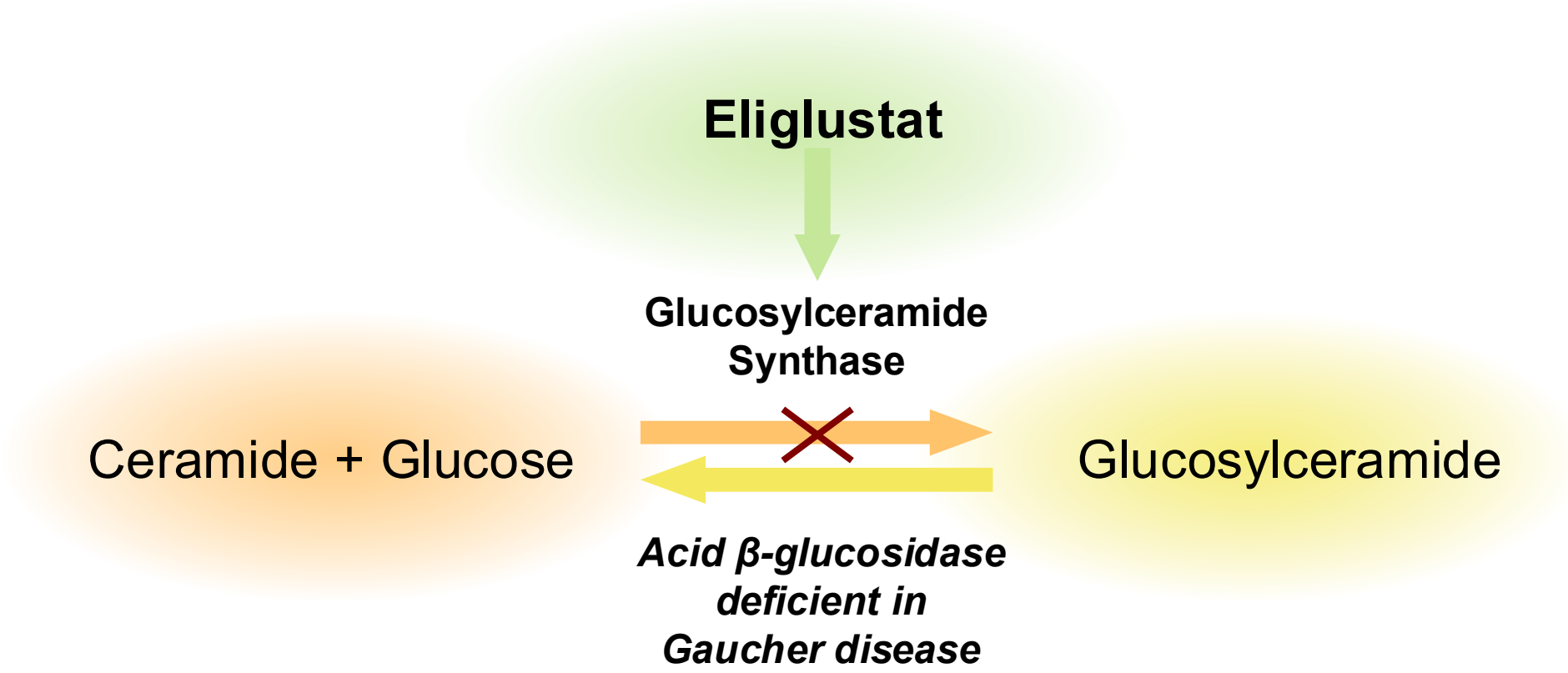
- Approved in EU & US for Gaucher disease when ERT is not possible
- Adverse effects: peripheral neuropathy (numbness, tingling, tremors), GI, visual, & cognitive complications

Eliglustat - Cerdelga

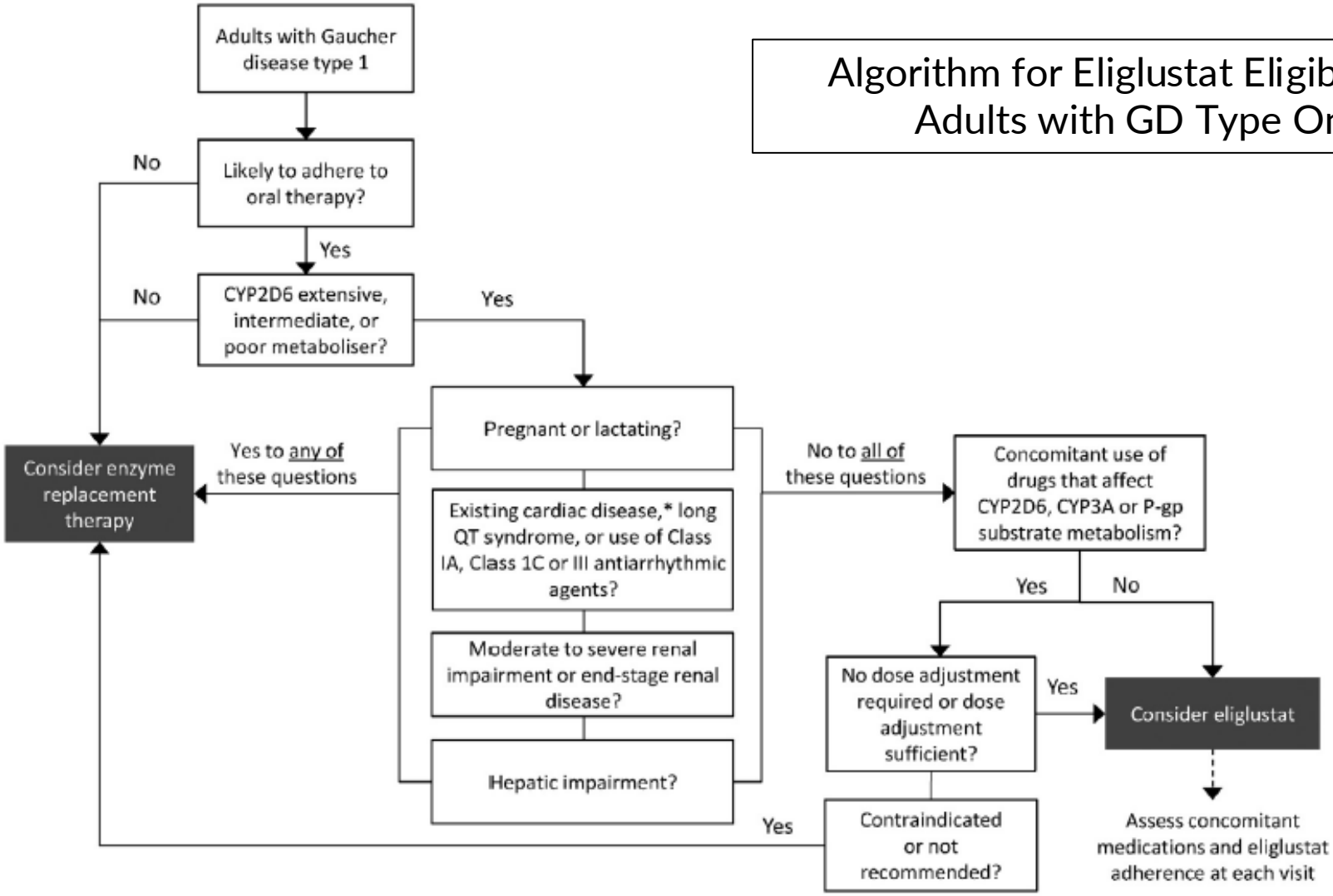
- Ceramide-based inhibitor
- FDA approved in August 2014

Eliglustat (Cerdelga) Mechanism of Action

Eliglustat inhibits glucosylceramide synthase, resulting in decreased production of glucosylceramide



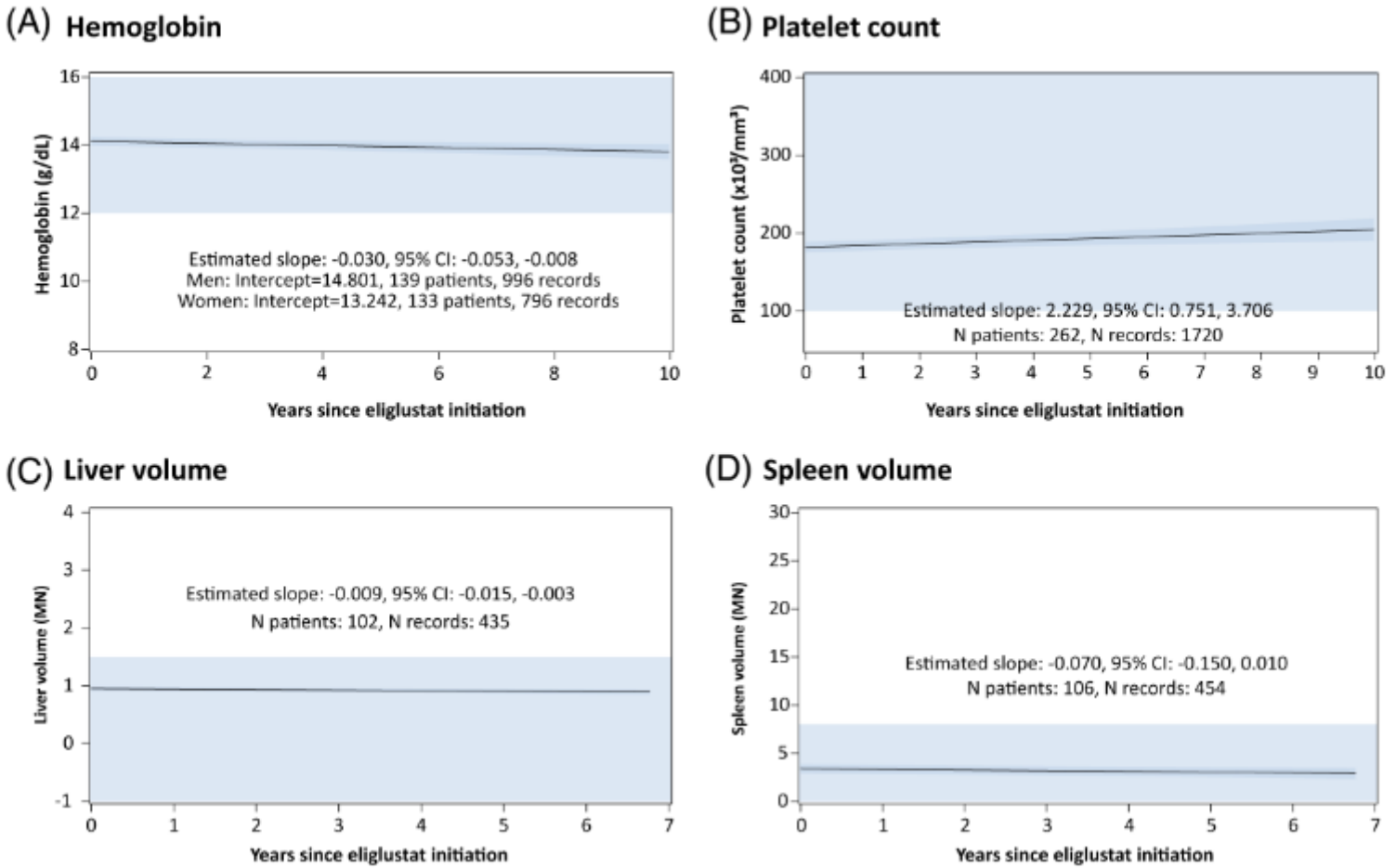
Algorithm for Eliglustat Eligibility in Adults with GD Type One



* Congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia.

Fig. 1. Algorithm to determine eligibility for eliglustat therapy in adults with Gaucher disease type 1.

Long-term effectiveness of eliglustat treatment: A real-world analysis from the International Collaborative Gaucher Group Gaucher Registry



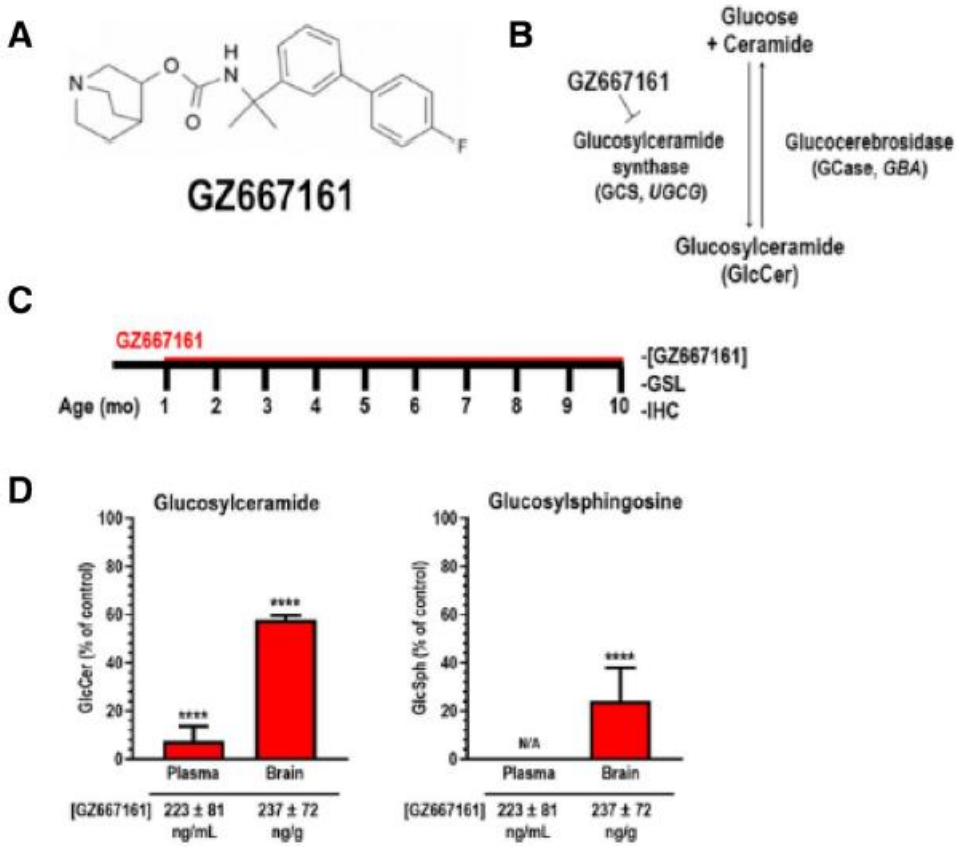
Non-splenectomized switch patients

Mistry et al. Am J hematol 2024

Choice of therapy

- Safety
- Lifestyle
- Compliance
- CYP2D6 status (Eliglustat)
  - Ultra Rapid metabolizer (not eligible)
- Drug interactions
- Pregnancy
  - Can only use ERT

Therapies in clinical development



VENGLUSTAT: An oral brain-penetrant substrate reduction therapy

LEAP2MONO trial

Primary Endpoint Met: Venglustat showed superior improvement in neurological symptoms (measured by SARA and RBANS) compared to ERT at 52 weeks.

Additional Considerations

Gaucher Disease in Pregnancy

- Women with GD are at increased risk for postpartum hemorrhage, postpartum infection, and bone disease
  - Hematology evaluation often recommended prior to delivery
  - Possible need for hemostatic support
- Increased monitoring is recommended with hemoglobin, platelets, biomarkers every 3 months
- ERT is treatment of choice (SRT not approved in pregnancy)

Gaucher Disease & Parkinson's Disease

- Both homozygote and heterozygote carriers of *GBA1* mutations are at increased risk for developing PD.
- 5% - 10% of individuals with PD have a *GBA1* mutation, making it the most common genetic risk factor.
- Specific *GBA* mutations & the likelihood of developing PD:
  - Severe GBA mutations (84GG, IVS2 + 1, V394L, D409H, L444P, RecTL → 13.6-fold increase PD risk
  - Mild mutations (N370S, R496H) → 2.2-fold increase risk

Table 2. Age-Specific Risk (Penetrance) for Parkinson Disease Among Ashkenazi Jewish Individuals With and Without *GBA* Mutations Using Kaplan-Meier Plots

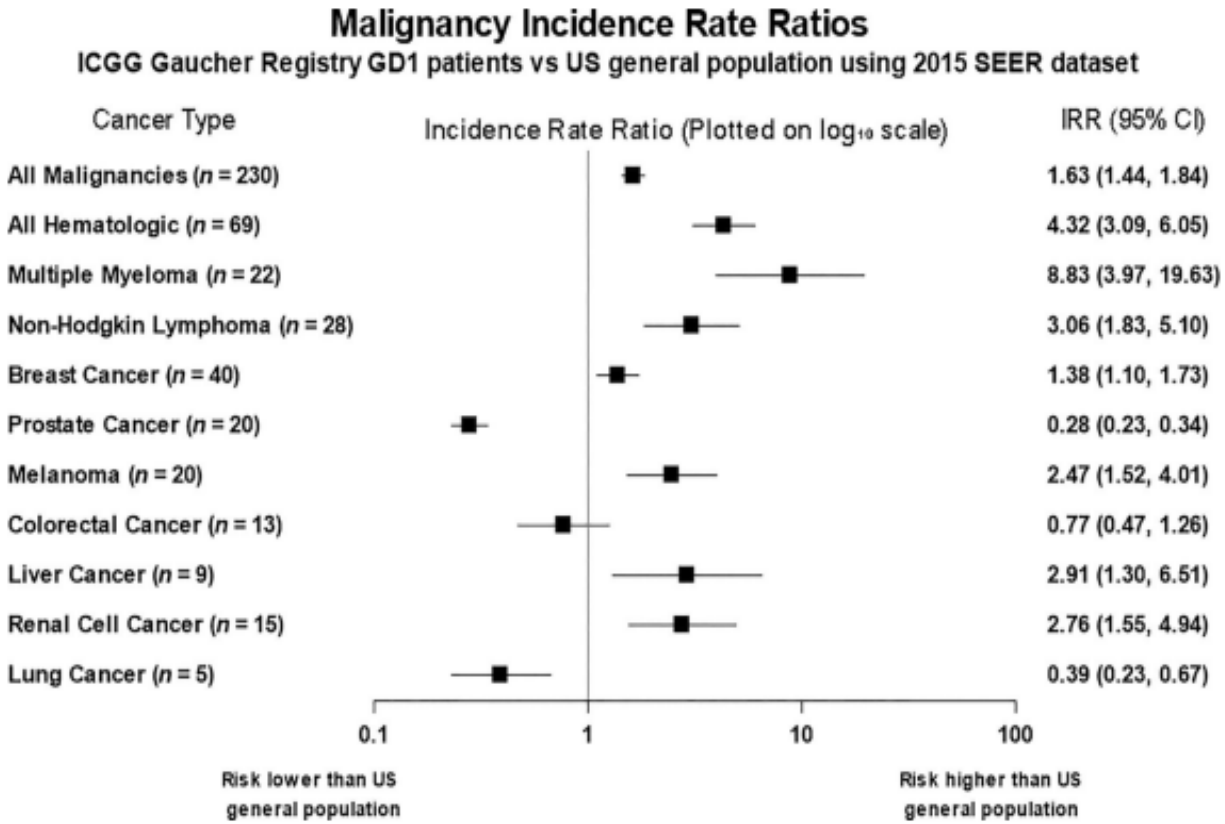
Genetic Group	Age-Specific Risk, % (95% CI)		
	60 y	70 y	80 y
Noncarriers (n = 154)	0.7 (1.37)	0.7 (1.37)	2.1 (2.94)
Obligate *GBA* carriers (n = 694)	1.5 (0.98)	5.2 (1.96)	7.7 (2.74)
Obligate N370S carriers (n = 464)	1.2 (0.98)	3.5 (1.96)	5.9 (3.14)
Patients with GD (N370S homozygotes or compound heterozygotes) (n = 427)	4.7 (3.33)	9.1 (6.07)	9.1 (6.07)

Average age of onset for GD patients is 54.2 years

Alcalay RN, JAMA Neurol. 2014

Malignancy in Gaucher Disease

- Multiple factors promote carcinogenesis in GD
  - Chronic lipid-mediated metabolic inflammation
  - Chronic B-cell stimulation
  - Metabolic derangements
- Hematologic malignancies are best described
  - Multiple myeloma (9-fold increased risk)
  - Non-hodgkin lymphoma (3-fold increased risk)



Rosenbloom BE, Am J Hematol. 2022

Hematologic Malignancy in Gaucher Disease

- Macrophage CD1d-presented glucosylsphingosine antigen results in polyclonal B-cell activation via Type II NKT cells and hypergammaglobulinemia
- Polyclonal → MGUS → Myeloma
- MGUS occurs more frequently at younger ages in GD patients
- GD treatment may impact risk
  - ERT reduces polyclonal hypergammaglobulinemia, but does not eliminate MGUS once it has developed
  - SRT reduces clonal immunoglobulin levels in patients with MGUS – may be helpful for prevention (preclinical data)
- Given association with B-cell malignancies, surveillance with immunoglobulin profile is recommended:
  - At GD diagnosis
  - Every 2 years for patients <50 years old
  - Annually for patients >50 years old

Nair S, et al. Mol Genet Metab. 2020

Key Takeaways

- Gaucher disease is an autosomal recessive lysosomal storage disorder resulting in multisystemic disease
- Clinical manifestations are heterogeneous, but commonly include cytopenias, bone disease, hepatosplenomegaly, and fatigue
- Enzyme testing is the gold standard for diagnosis, with confirmatory *GBA1* testing and supportive biomarkers, such as lyso-GL1
- Treatment is individualized and includes enzyme replacement therapy (ERT) and substrate reduction therapy (SRT)
- Gaucher disease is associated with increased risks for bleeding in pregnancy, Parkinson's disease, and hematologic malignancies requiring long-term surveillance

Thank you.

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