Rare Diagnoses Hidden in Plain Sight: Lysosomal Storage Diseases in Oncology

Coy Heldermon, M.D., Ph.D.

Pediatric Multi-disciplinary LSD clinic

Neurology
Cardiology
Pulmonology
Rehabilitation
Physical Therapy
Occupational Therapy

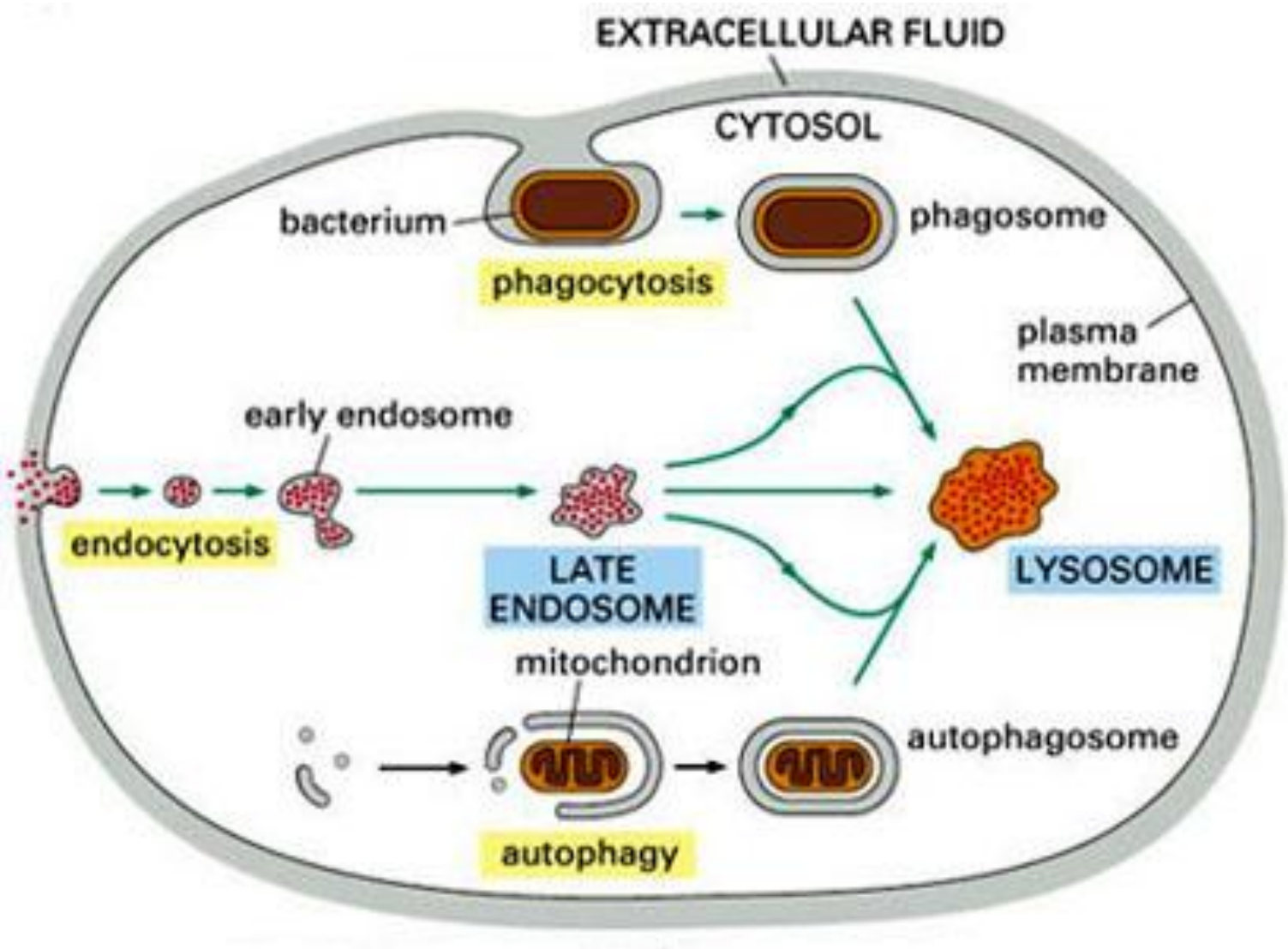
352-294-5757

Adult Multi-disciplinary LSD clinic

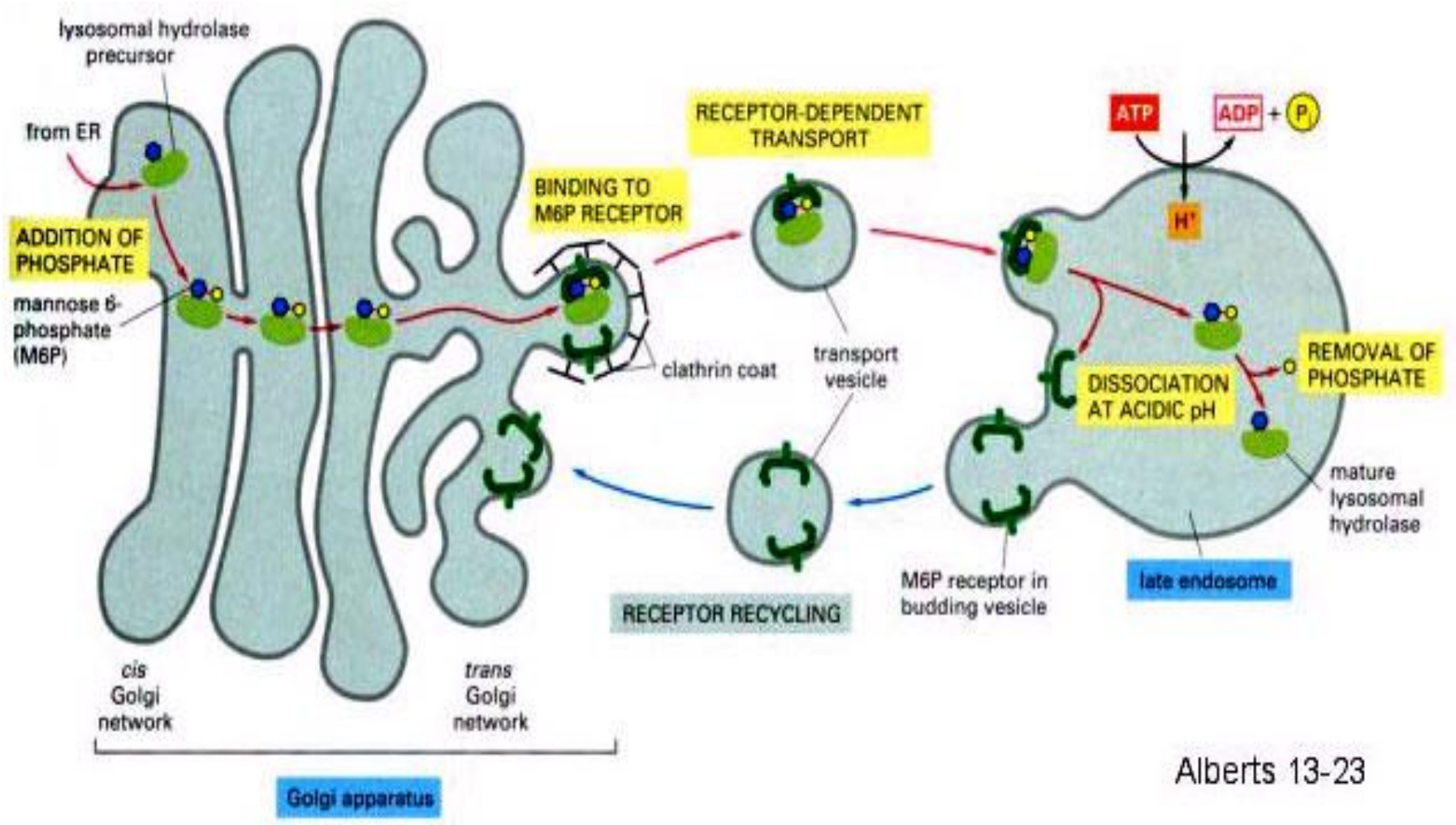
Nephrology
Hematology/Oncology
Neurology
Genetic Counseling
Pulmonology

phone 352-265-8199
fax 352-627-4932

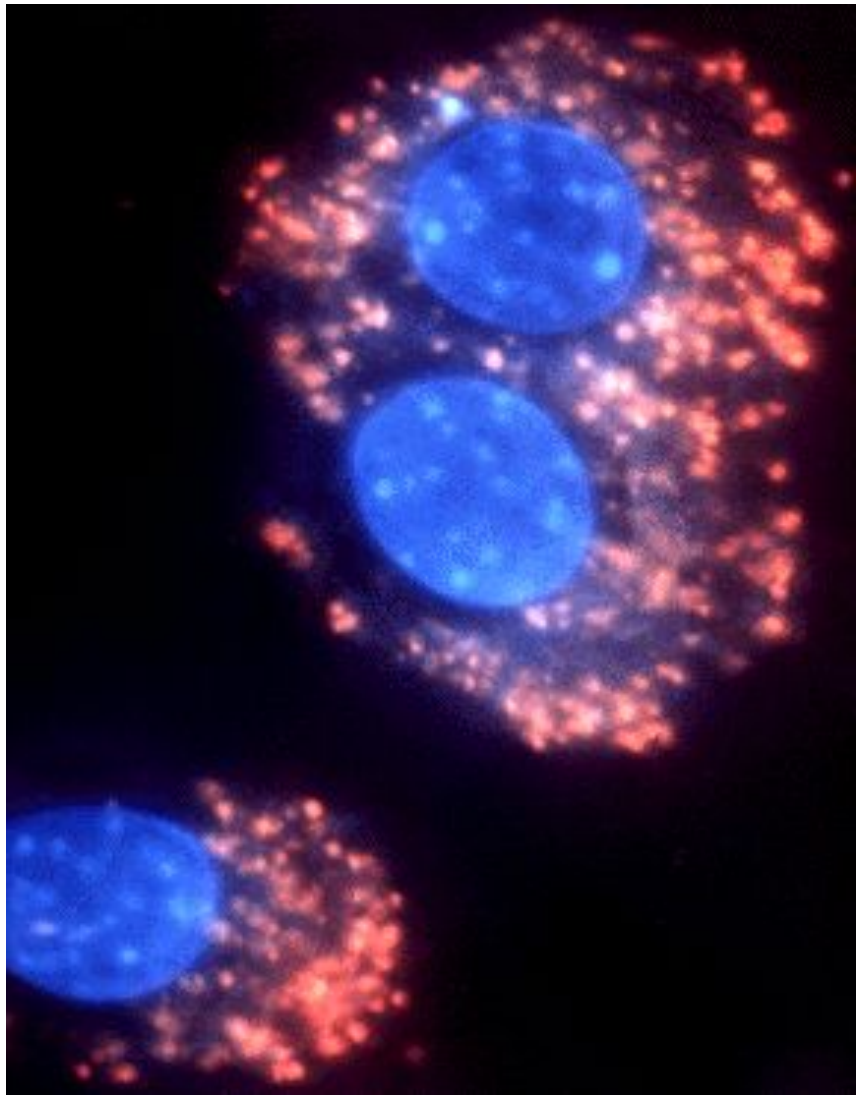
lysosomal function



Usually the protein is targeted to the lysosome by M6PR



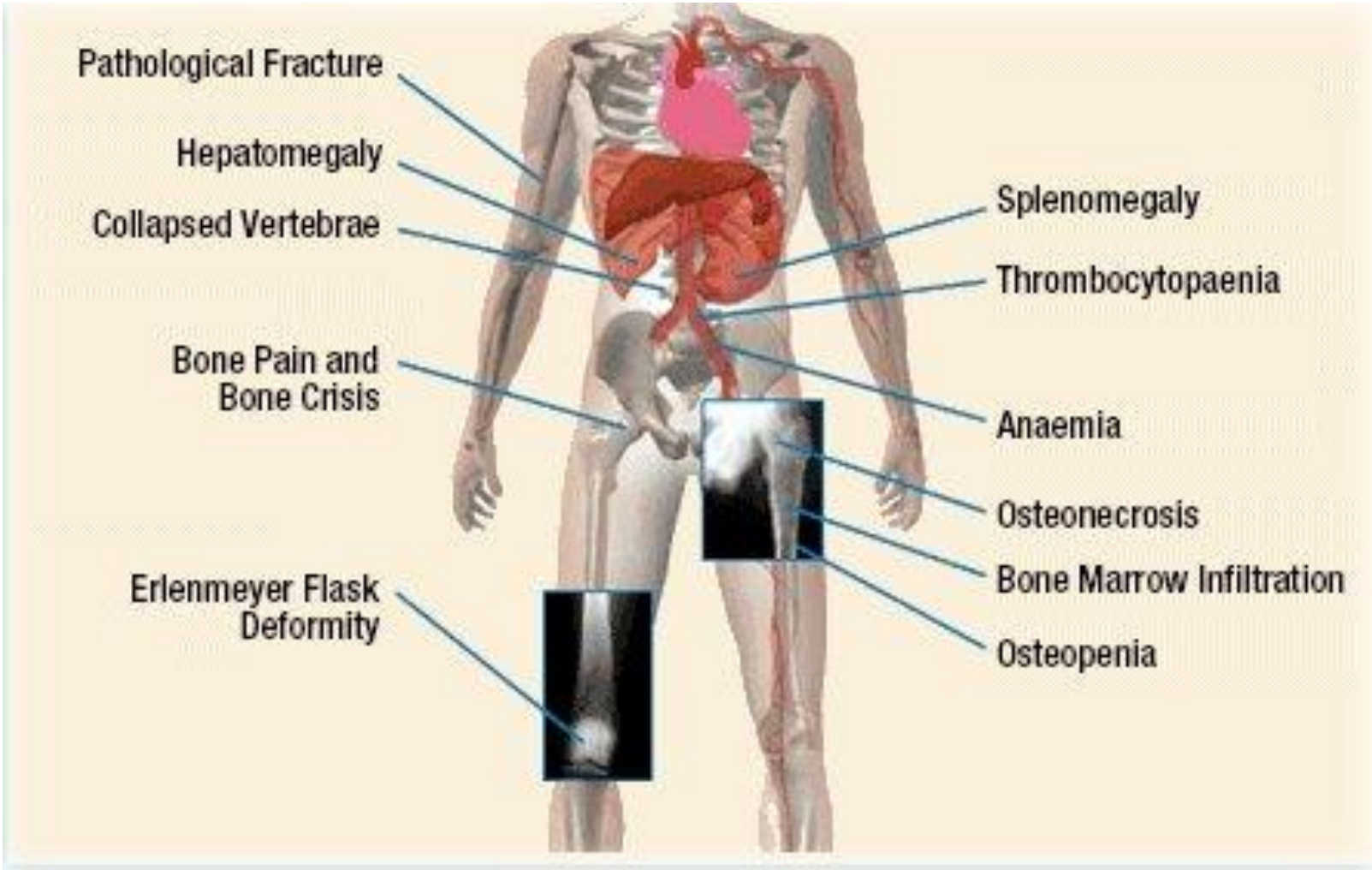
The lysosomes are abundant



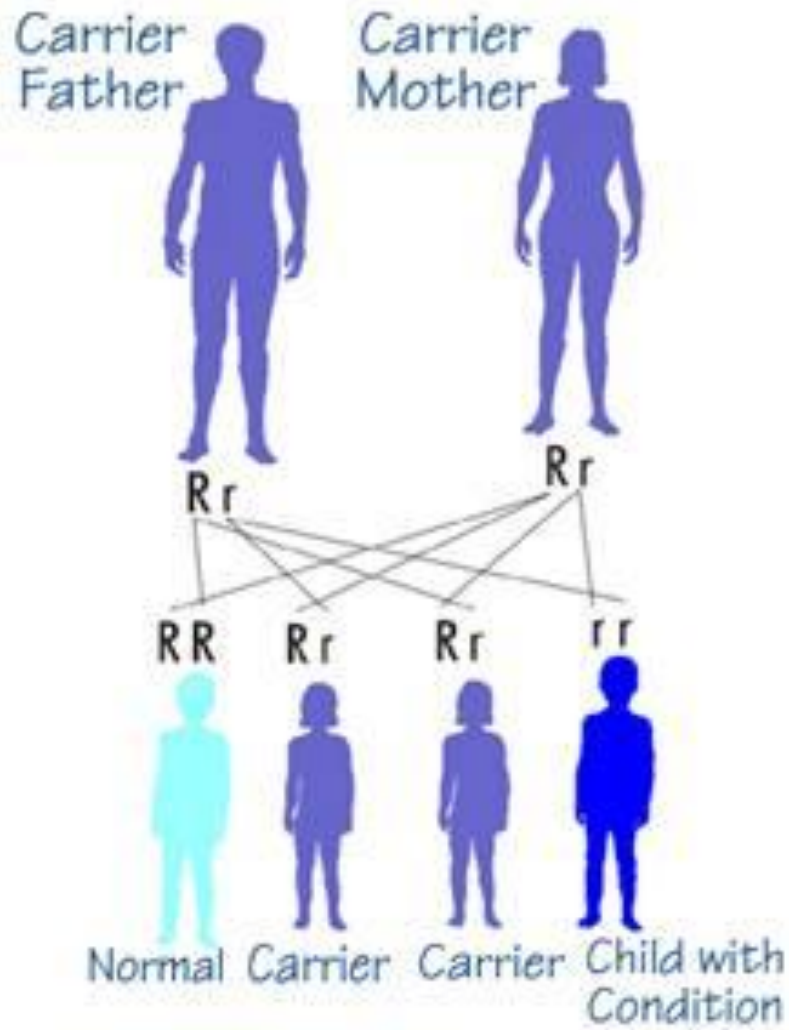
Lysosomal Storage Diseases

- **Glycogen storage disease type II (alpha-glucosidase)**
- Mucopolysaccharidoses
  - **MPS type IH, Hurler syndrome (alpha-L-iduronidase)**
  - **MPS type I H/S, Hurler-Scheie syndrome**
  - **MPS type I S, Scheie syndrome**
  - **MPS type II A, Hunter syndrome, severe (iduronate sulfatase)**
  - **MPS type II B, Hunter syndrome, mild (iduronate sulfatase)**
  - **MPS type III A-D, Sanfilippo syndrome (heparan *N*-sulfatase)**
  - MPS type IV A, Morquio syndrome, classic (galactose 6-sulfatase)
  - **MPS type VI, Maroteaux-Lamy syndrome (arylsulfatase B)**
  - MPS type VII, Sly syndrome (beta-glucuronidase)
- Mucolipidosis II (I-cell disease) and mucolipidosis III (phosphotransferase)
- Schindler disease/Kanzaki disease (alpha-*N*-acetylgalactosaminidase)
- Glycoprotein degradation
- Alpha-mannosidosis and beta-mannosidosis
- Fucosidosis
- Sialidosis
- Aspartylglucosaminuria (AGU)
- Carbohydrate-deficient glycoprotein syndrome
- Wolman and cholesterol ester storage disease (acid lipase)
- Farber disease, disseminated lipogranulomatosis (ceramidase)
- Niemann-Pick disease
  - Niemann-Pick disease type A (sphingomyelinase)
  - **Niemann-Pick disease type B (sphingomyelinase)**
  - **Niemann-Pick disease C1 (NPC1)**
  - Niemann-Pick disease C2
- **Gaucher disease types I, II, and III (beta-glucosidase)**
- Krabbe disease, infantile globoid-cell leukodystrophy (galactosylceramidase)
- **Fabry disease (alpha-galactosidase A)**
- Multiple sulfatase deficiency (sulfatases)
- GM1 gangliosidosis and Morquio B disease (beta-galactosidase)
- Galactosialidosis (protective protein)
- GM2 gangliosidosis, Tay-Sachs and Sandhoff diseases (hexosaminidase)
- Cystinosis (cysteine transporter)
- Sialic acid storage disease (sialic acid transporter)
- Pyknodysostosis (cathepsin K)
- Metachromatic leukodystrophy (galactose-3-sulfatase)
- Galactosialidosis (neuraminidase, beta-galactosidase, protective protein)
- Neuronal ceroid lipofuscinosis, infantile (palmityl protein thioesterase)
- **Neuronal ceroid lipofuscinosis, late infantile (carboxypeptidase)**
- Cobalamin deficiency type F (cobalamin transporter)

Gaucher's Disease



Autosomal Recessive Inheritance

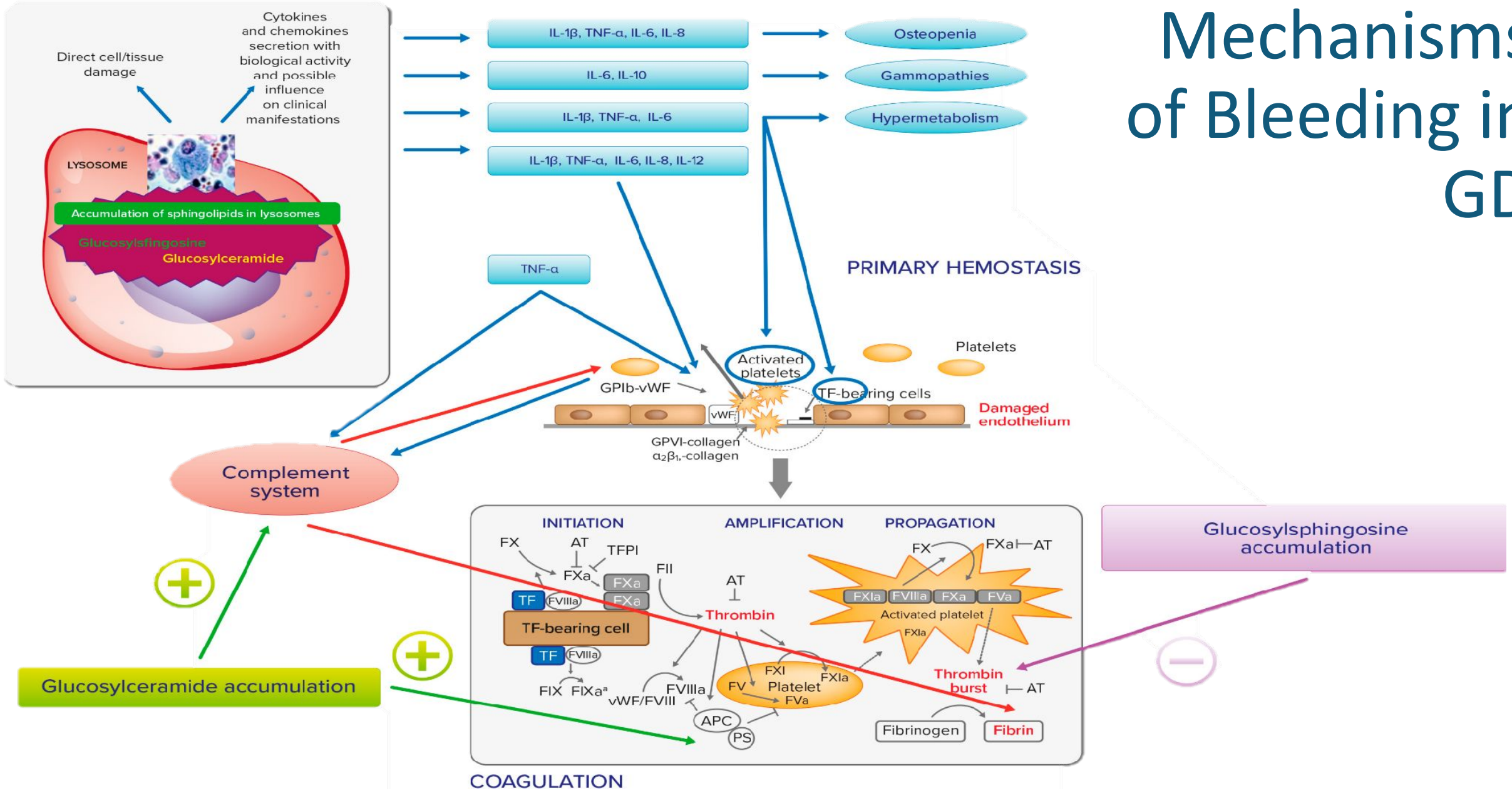


Traditional GD Classifications

Gaucher Disease	Type 1 Non-neuronopathic	Type 2 **Acute Neuronopathic**	Type 3 Chronic Neuronopathic
Epidemiology (Prevalence)	Panethnic (~1:60,000) ↑ in Ashkenazi Jewish descent (~1:850)	Panethnic (~1:500,000)	Panethnic (~1:100,000) ↑ in Middle East, North Europe, and Asia
Age of Onset (Lifespan)	Childhood to adulthood (variable)	Infancy (< 2 years)	Infancy to early childhood (3rd to 5th decade)
% of GD	~90-95%	< 5%	~5-10%
Characteristic Manifestations	**All**: anemia, thrombocytopenia, splenomegaly, hepatomegaly, bone pain/abnormalities		
	Delayed growth/puberty (children), gammopathy, hyperferritinemia	Rapid progressive neurological deterioration	Oculomotor disturbances, epilepsy, ataxia, kyphosis **3a**: neuro dominant **3b**: visceral/skeletal dominant **3c**: cardiovascular involvement

Charrow J, et al. *Arch Intern Med*. 2000;160(18):2835-2843. Nalysnyk L, et al. *Hematology*. 2017;22(2):65-73. Wang M, et al. *J Pediatr Hematol Oncol*. 2022;10.1097/MPH.0000000000002506. Stirnemann J, et al. *Int J Mol Sci*. 2017;18(2):441.

Mechanisms of Bleeding in GD



Linari S, Castaman G. *J Clin Med*. 2022;11(23):6920.

Hemostatic Dysfunction in GD

- **Pre-initiation of disease directed therapy (DDT)**
  - Thrombocytopenia and related clotting factor deficits may contribute to bleeding (usually minor) usually improves with therapy
- **Post-initiation of DDT**
  - 1/3rd - 2/3^{rds} have persistent platelet aggregation defects by PFA-100 increased bleeding risk during pregnancy delivery, dental procedures, surgeries, etc.
  - 1/3rd – 1/2 have increased D-dimer and decreased ADAMTS13 may confound DVT/PE or inpatient bleeding assessments when sick
  - Up to 1/2 have persistent mild to moderate clotting factor deficiencies, especially V, X, XI, XII

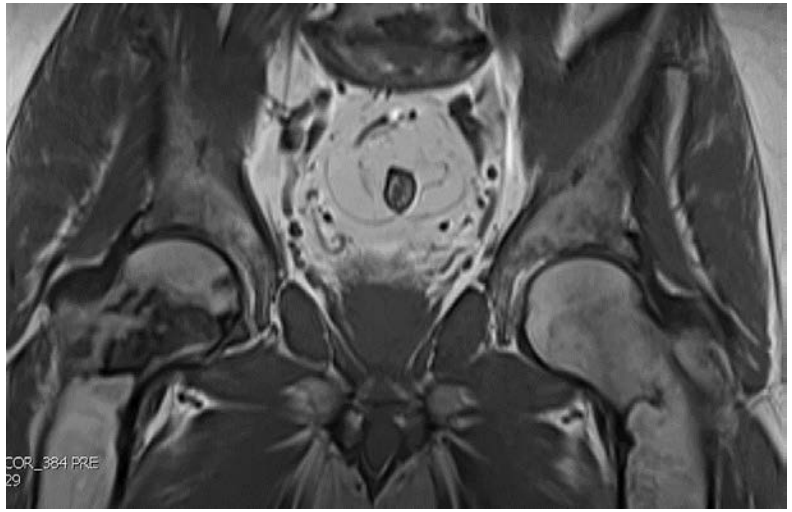
PFA-100 = Platelet Function Analyzer, ADAMTS13 = von Willebrand factor-cleaving protease, DVT/PE = deep vein thrombosis / pulmonary embolism.

Mitrovic M, et al. *Platelets*. 2012;23(2):143-149. Giona F, et al. *J Thromb Haemost*. 2006;4(8):1831-1833. Komninaka V, et al. *Blood Cells Mol Dis*. 2020;80:102371. Simchen MJ, et al. *Thromb Haemost*. 2011;105(3):509-514. Serratrice C, et al. *J Hematol*. 2019;8(3):121-124.

Bone Abnormalities

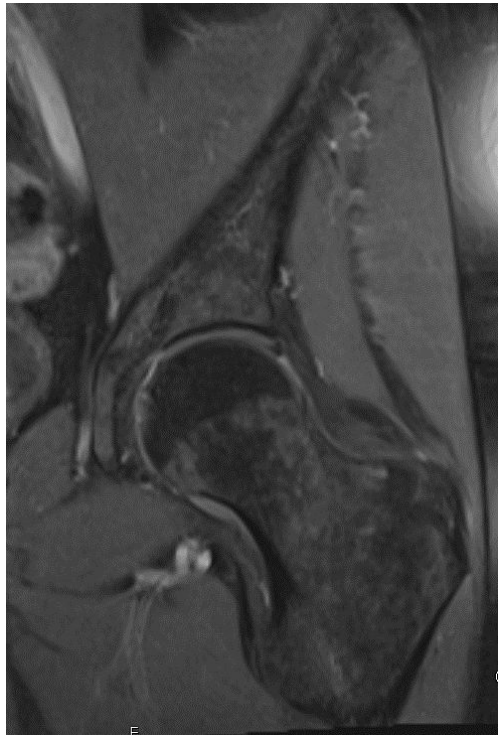
Some degree of bone abnormalities are present in vast majority of GD, e.g., osteonecrosis, Erlenmeyer flask deformity, lytic lesions, bone marrow infiltration, avascular necrosis, osteoporosis.

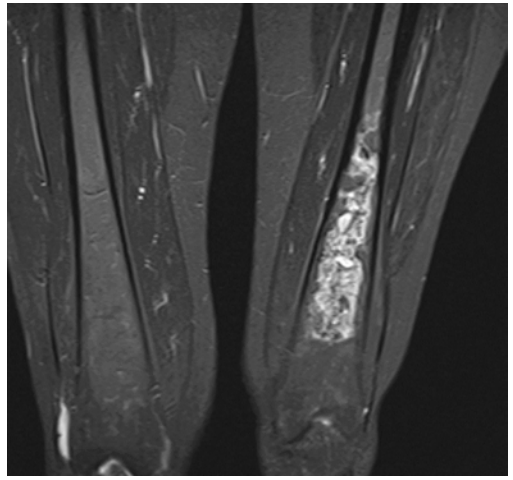
Note: Bone pain/infarcts may improve with DDT but may not completely resolve, and will possibly worsen with splenectomy

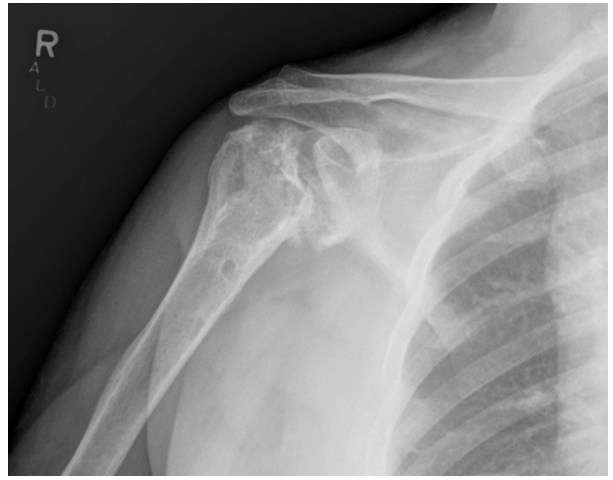


(a) MRI showing bilateral femoral head and iliac infarcts

(b) Iliac and femoral head infarcts with necrosis and marrow infiltration







(c) MRI showing distal left femoral diaphysis medullary infarct and Erlenmeyer flask deformities

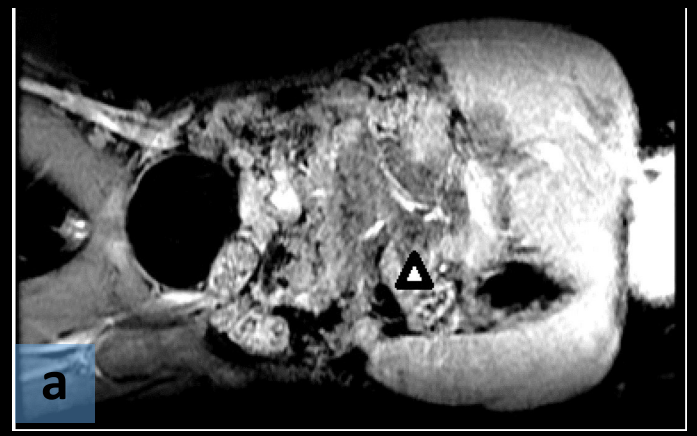
(d) X-ray showing humeral head infarct leading to abscess and effacement of humeral head, right shoulder immobilization

Marcucci G, et al. Calcif Tissue Int. 2014;95(6):477-494. Piran S, et al. *Blood Cells Mol Dis*. 2009;43(3):289-293. Cappellini MD, et al. *Blood Cells Mol Dis*. 2023;98:102705. Charrow J, et al. *Clin Genet*. 2007;71(3):205-211

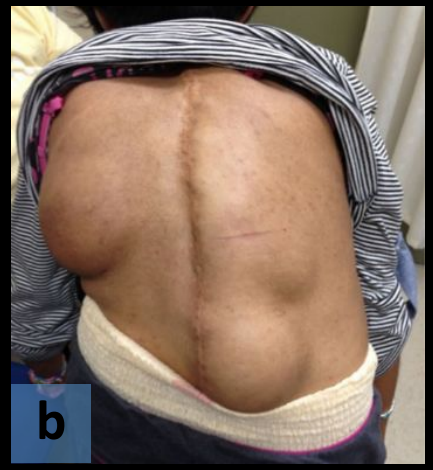
Gaucheromas

Gaucheroma: slow growing mass or “pseudotumor” of Gaucher cells

- Primarily found in mesenteric and mediastinal lymph nodes, but also reported in liver, spleen, bone, soft tissue, sub-retina, and abdomen
- Serious complications include protein-losing enteropathy and mesenteric lymphadenopathy, but full clinical significance is unknown
- Little evidence-based guidance regarding diagnosis and management, but appears to respond to SRT over ERT



(a) Abdominal MRI showing multiple clustered enlarged lymph nodes at mesentery (arrow), several small lymph nodes at bilateral inguinal regions secondary to Gaucheroma



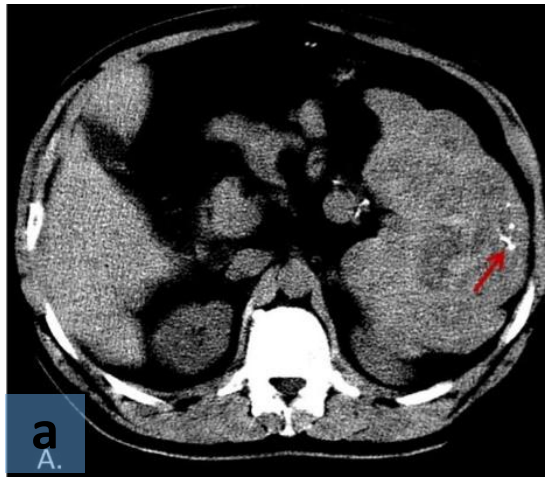
(b) 30yo female with GD presenting with several slow growing soft-tissue masses along back, later confirmed to be Gaucheromas

Yano S, et al. *J Pediatr Genet*. 2020;11(1):47-50. Tseng SY, et al. *Mol Genet Metab Rep*. 2019;20:100489. Mahajan N, et al. *J Inherit Metab Dis*. 2016;39(6):887-888.

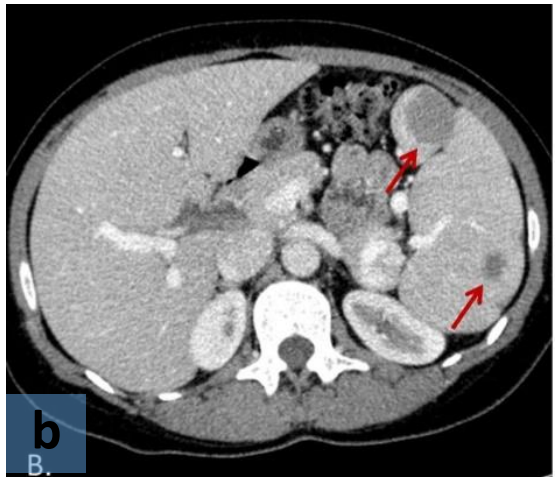
Hepatic and Splenic Lesions

Liver and spleen size monitoring can reveal lesions that may be hemangiomas, Gaucheromas, or hepatocellular carcinomas (HCC).

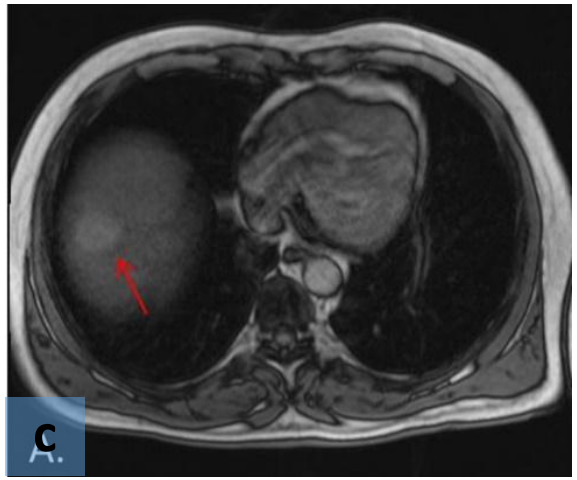
Note: Not all HCC lesions have typical HCC washout, need to biopsy!



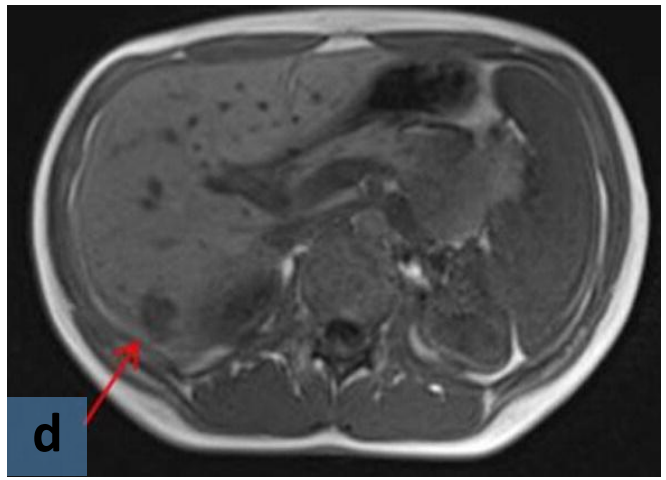
(a) CT of 54yo male showing multiple hypodense lesions and calcifications (arrow) in spleen



(b) CT of 35yo female showing two hypodensities in spleen



(c) T1 MRI of 62yo male showing hyperintense focal lesion in liver - differential diagnosis: FNH or Gaucheroma



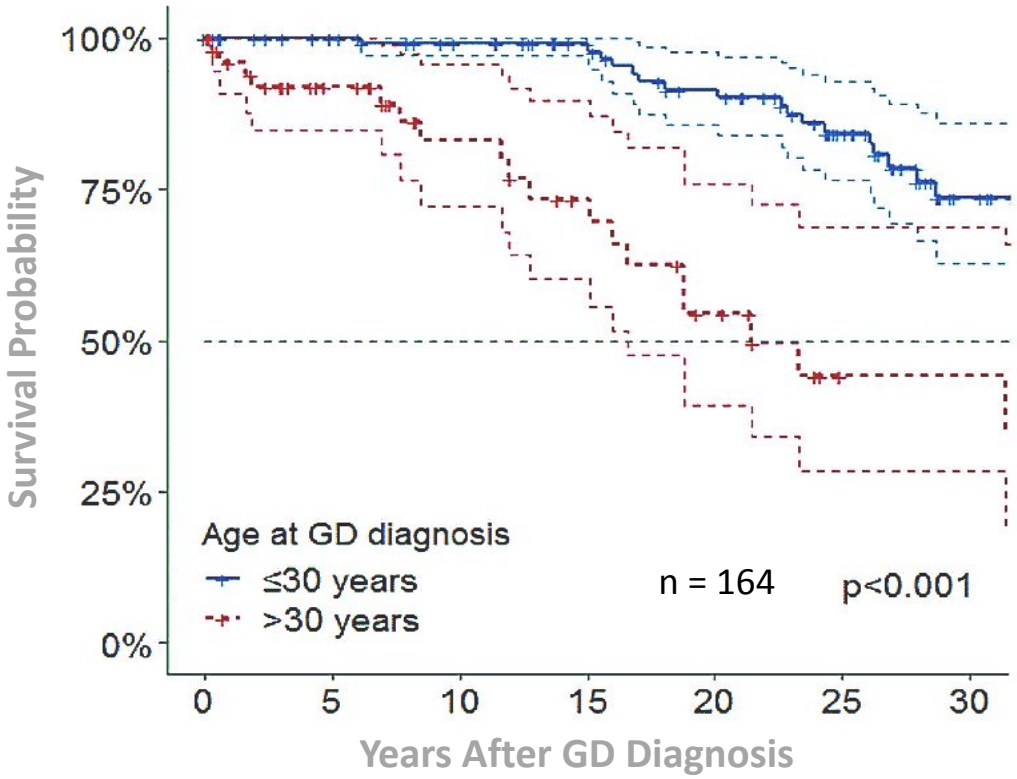
(d) T1 MRI of 28yo female showing hypointense lesion, differential diagnosis: hemangioma or Gaucheroma

yo = year old, MRI = magnetic resonance imaging, FNH = Focal Nodular Hyperplasia. Regenboog M, et al. *Blood Cells Mol Dis*. 2016;60:49-57.

Elevated Cancer Risk in GD

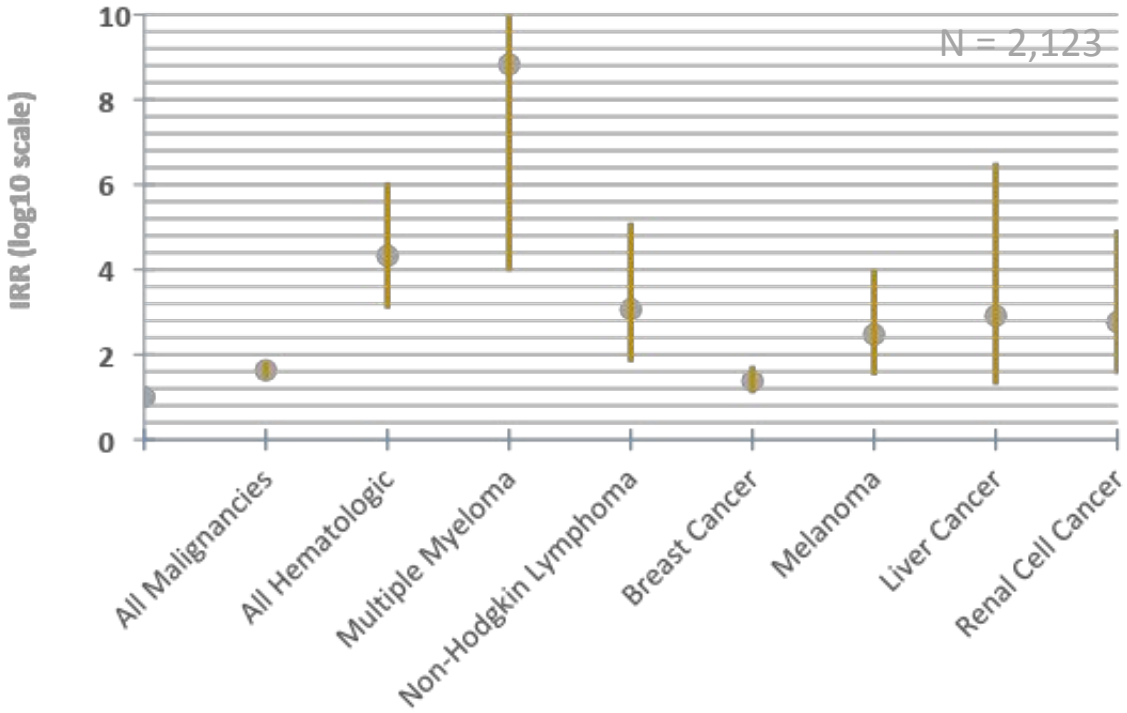
Survival Without Monoclonal Gammopathy in French GD Registry

Kaplein-Meier Estimates



Malignancy Incidence Rate Ratios (IRR)

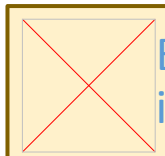
ICGG Gaucher Registry GD1 vs General Population



ICGG = International Collaborative Gaucher Group. Nguyen Y, et al. *Int J Mol Sci*. 2020;21(4):1247. Rosenbloom BE, et al. *Am J Hematol*. 2022;97(10):1337-1347. de Fost M, et al. *Blood Cells Mol Dis*. 2006;36(1):53-58

Heme/Onc Monitoring in GD

- **Liver and spleen imaging: annual monitoring preferred**
  - Size and lesion presence
  - Biopsy new liver lesions even if atypical washout on MRI
  - Periodically monitor liver elastography
- **CBC with differential: monitor every 3 – 6 months**
  - Cytopenias and malignancy indicators
- **CMP and SPEP or free light chain: monitor every 6 months**
  - Progression of gammopathy
  - LFT abnormalities
- **PFA/coagulation tests: check prior to any procedures prone to bleeding**
- **Bone assessment with pelvic MRI and skeletal survey: monitor every 1 – 2 years**
  - Marrow infiltration and avascular necrosis
  - Periodically assess bone density

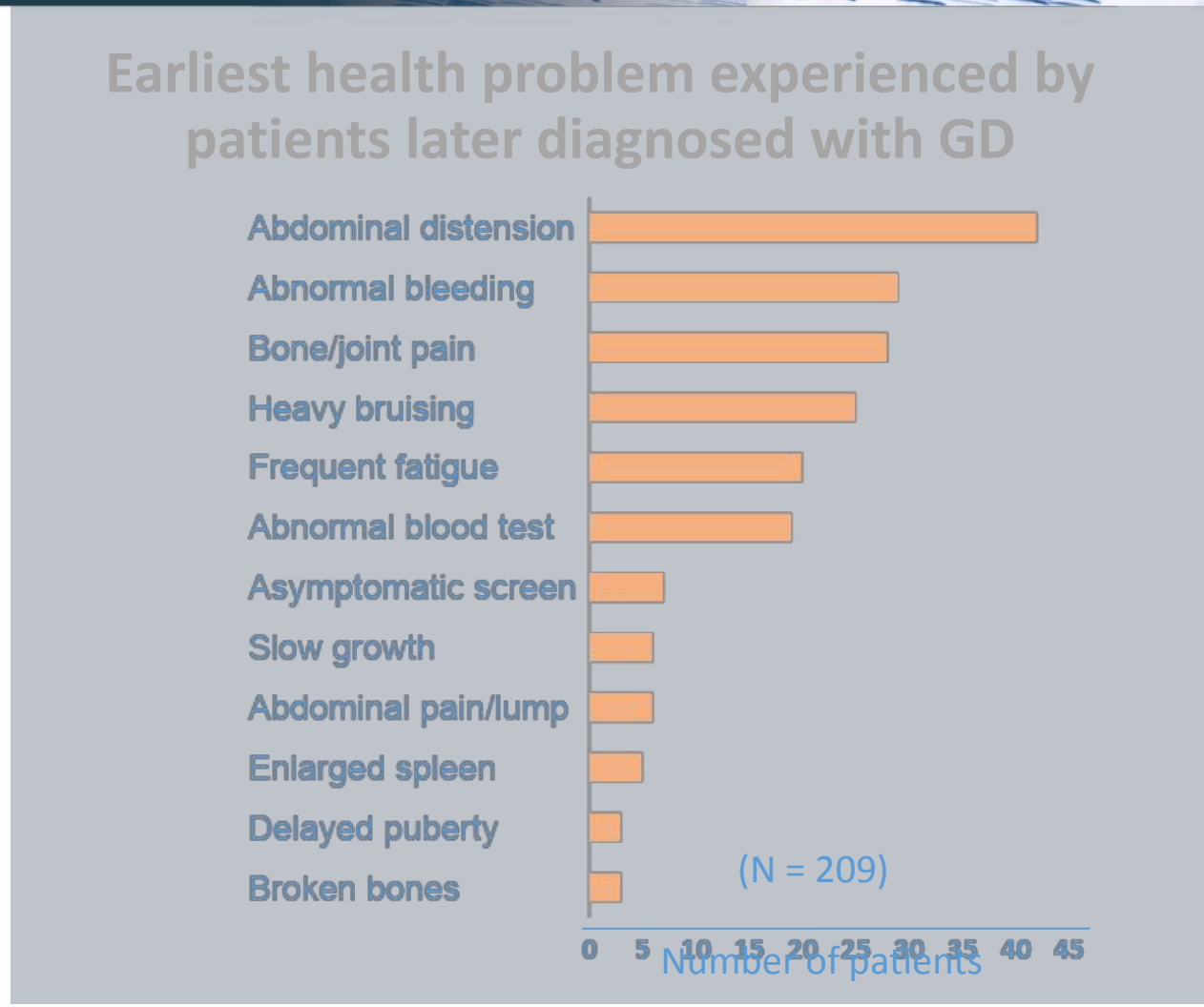


Encourage exercise to improve outcomes!

CBC = complete blood count, CMP = comprehensive metabolic panel, SPEP = serum protein electrophoresis, LFT = liver function tests, PFTs = pulmonary function tests, DLCO = diffusing capacity of carbon monoxide. Giraldo P, Andrade-Campos M. *J Blood Med*. 2021;12:1045-1056

GD Recognition and Diagnosis

- **Asymptomatic screening**
  - Newborn screening (not in RUSP, but done in some areas)
  - Genetic carrier testing (based on family history)
- **Diagnostic odyssey**
  - First manifestations seen by PCP/pediatrician usually non-specific or “atypical” for GD
  - Often referred to multiple specialists
  - Diagnosis frequently delayed until more characteristic manifestations develop/progress



RUSP = Recommended Uniform Screening Panel

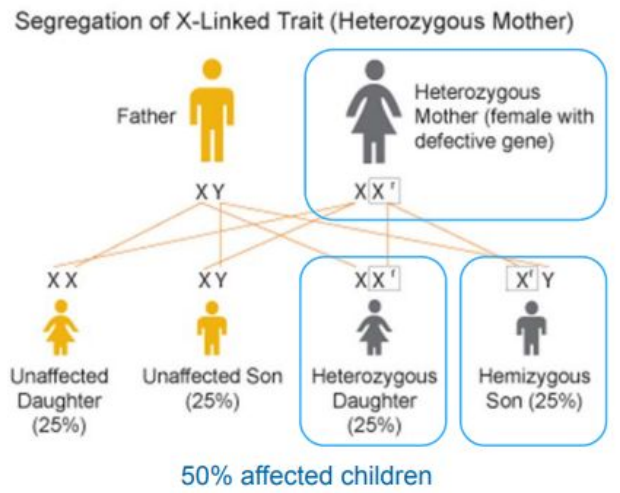
Mehta A, et al. *Mol Genet Metab*. 2017;122(3):122-129. Mehta A, et al. *Intern Med J.* 2019;49(5):578-591.

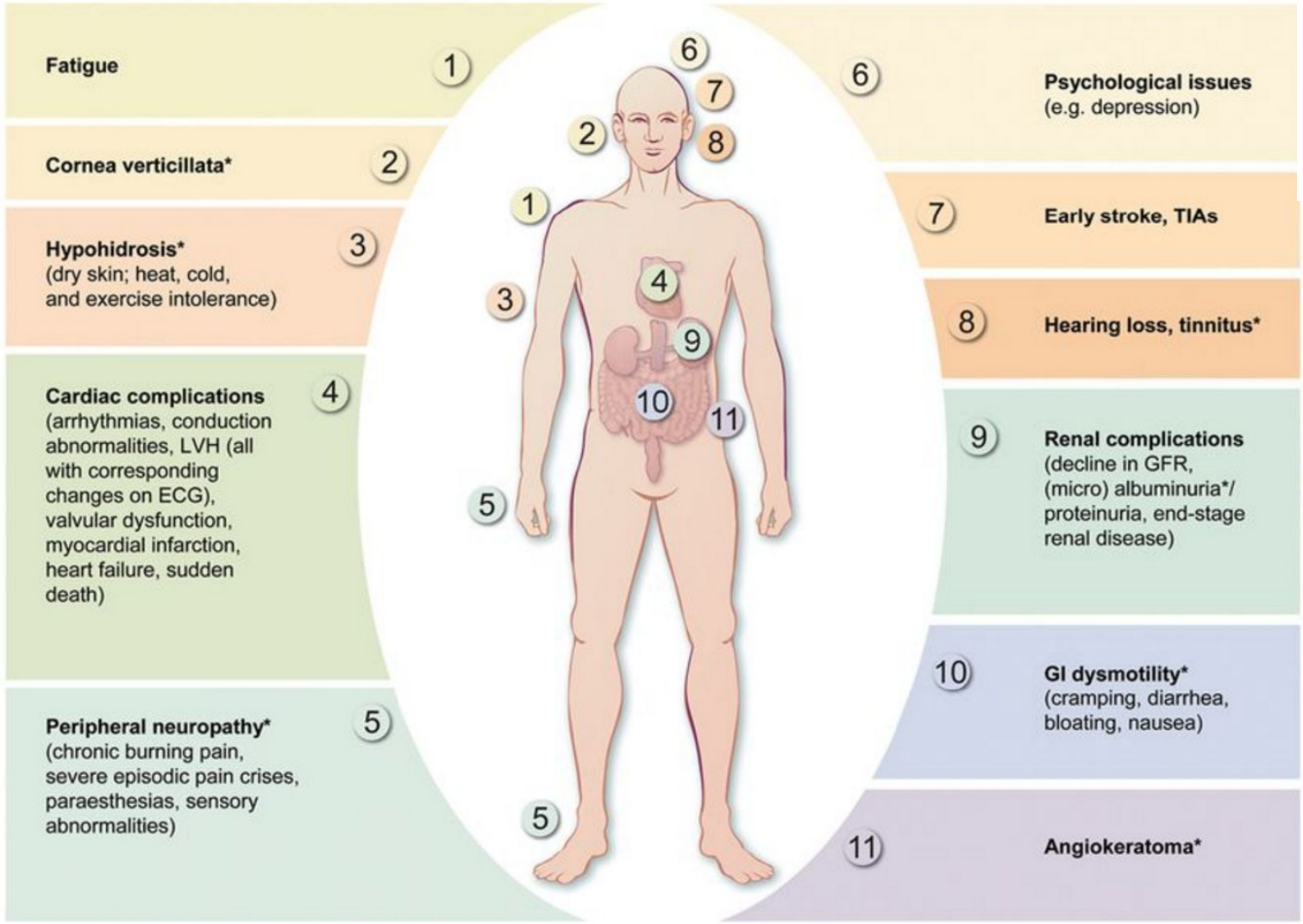
Treatments

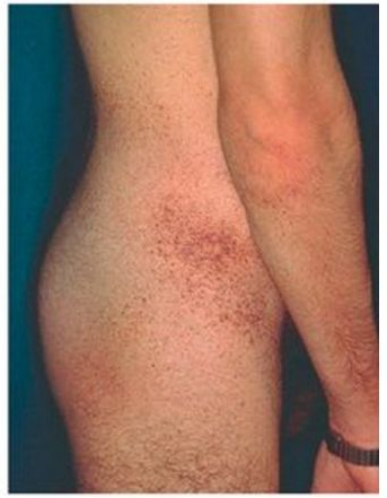
- Imiglucerase, velaglucerase or taliglucerase – 60 units/kg q 2 weeks
- Miglustat
- Eliglustat (dosing based on CYP2D6 genotype)
- Supportive care for bone, marrow and cancer.

Fabry Disease – X linked

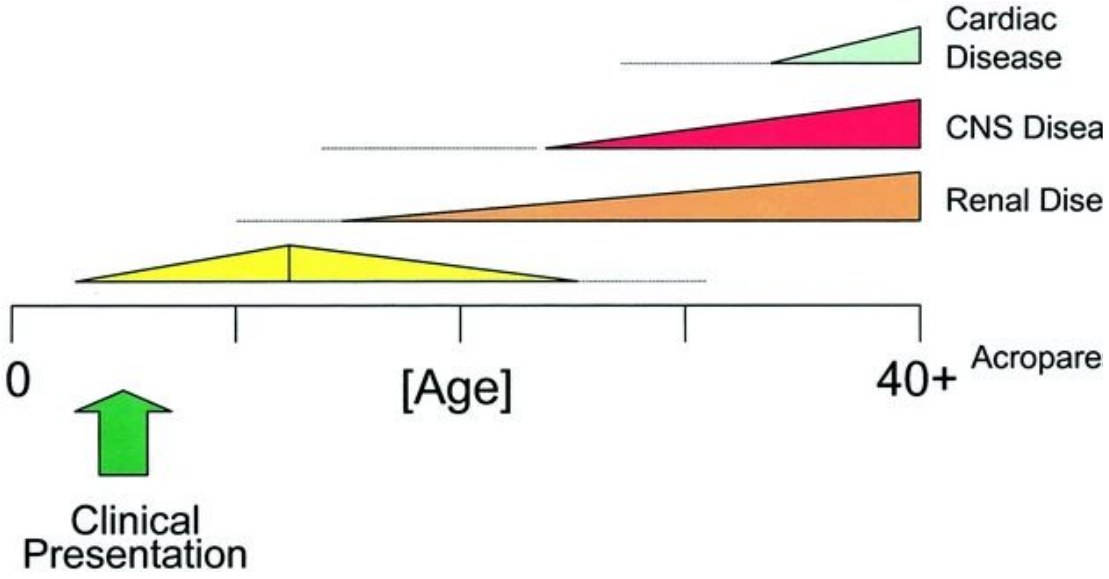
Deficiency of α-Gal A in Fabry disease leads to progressive accumulation of glycolipids



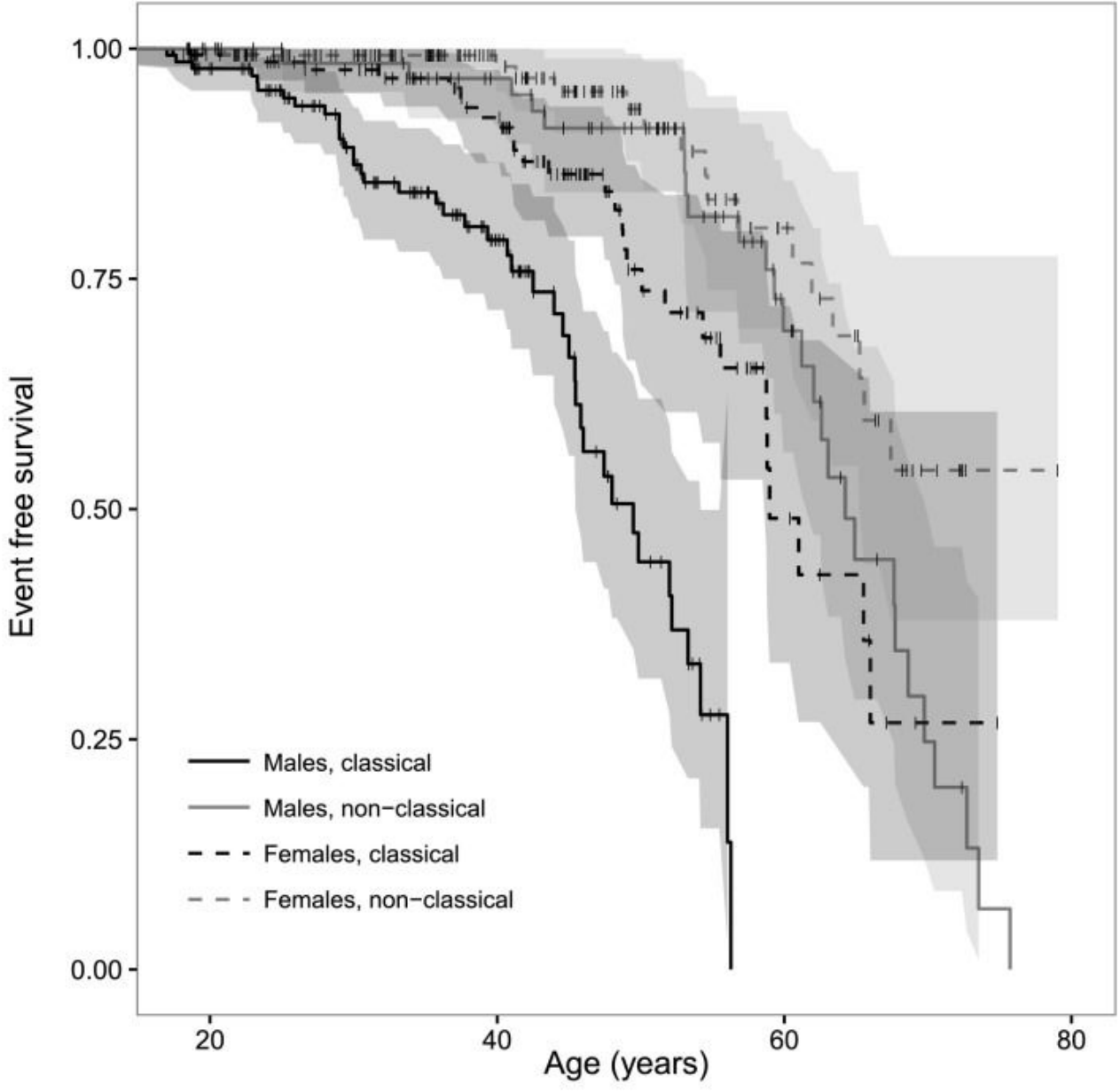




From Yousef, et al, European Heart Journal



Hopkin, R., Bissler, J. & Grabowski, G. Comparative evaluation of α-galactosidase A infusions for treatment of Fabry disease. *Genet Med* **5**, 144–153 (2003). https://doi.org/10.1097/00125817-200305000-00004

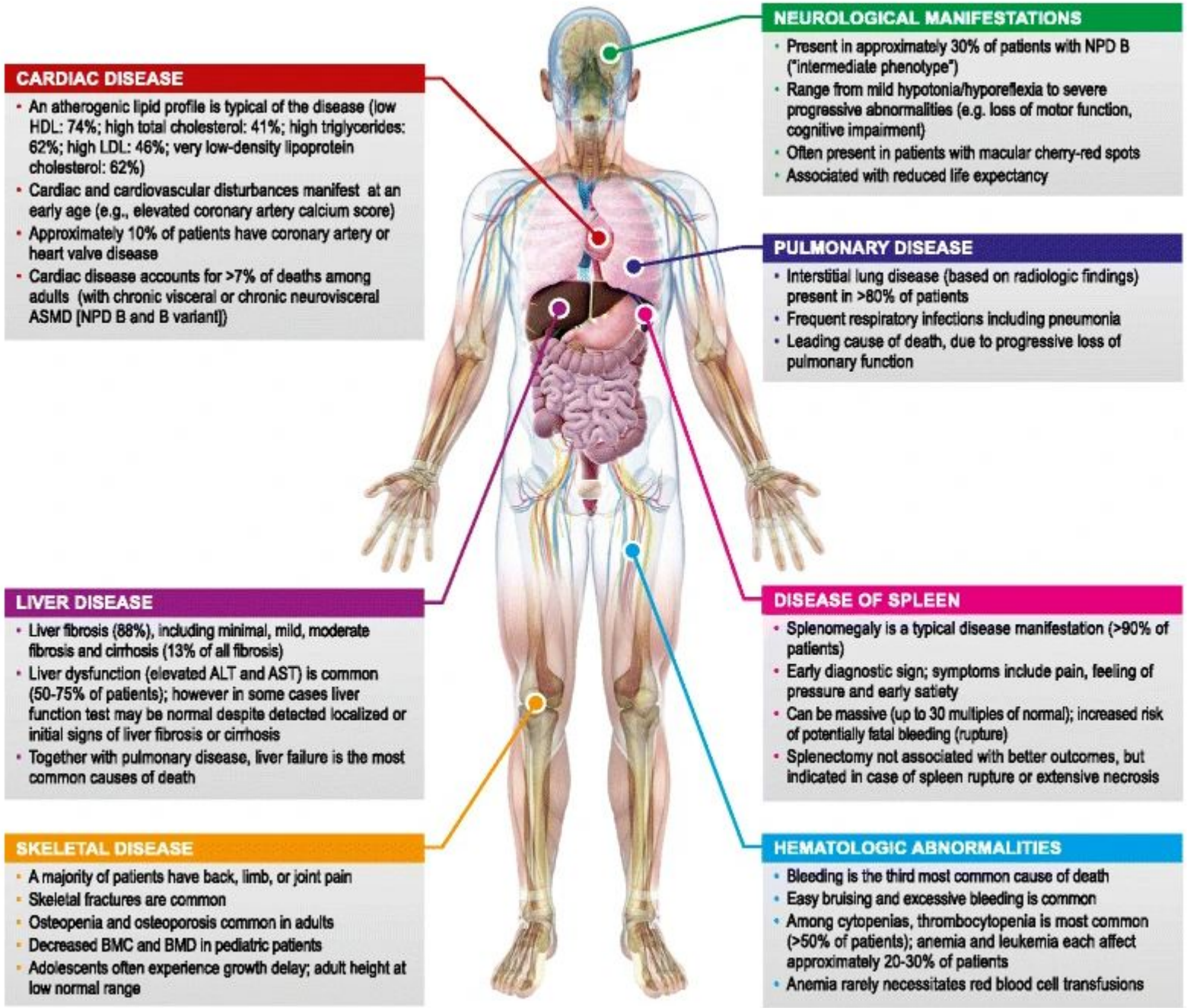


Males, classical	129	51	0	0
Males, non−classical	65	55	20	0
Females, classical	136	85	9	0
Females, non−classical	142	80	22	0

Arends M, Wanner C, Hughes D, Mehta A, Oder D, Watkinson OT, Elliott PM, Linthorst GE, Wijburg FA, Biegstraaten M, Hollak CE. Characterization of Classical and Nonclassical Fabry Disease: A Multicenter Study. J Am Soc Nephrol. 2017 May;28(5):1631-1641. doi: 10.1681/ASN.2016090964. Epub 2016 Dec 15. PMID: 27979989; PMCID: PMC5407735.

Niemann-Pick A/B – Acid Sphingomyelinase Deficiency

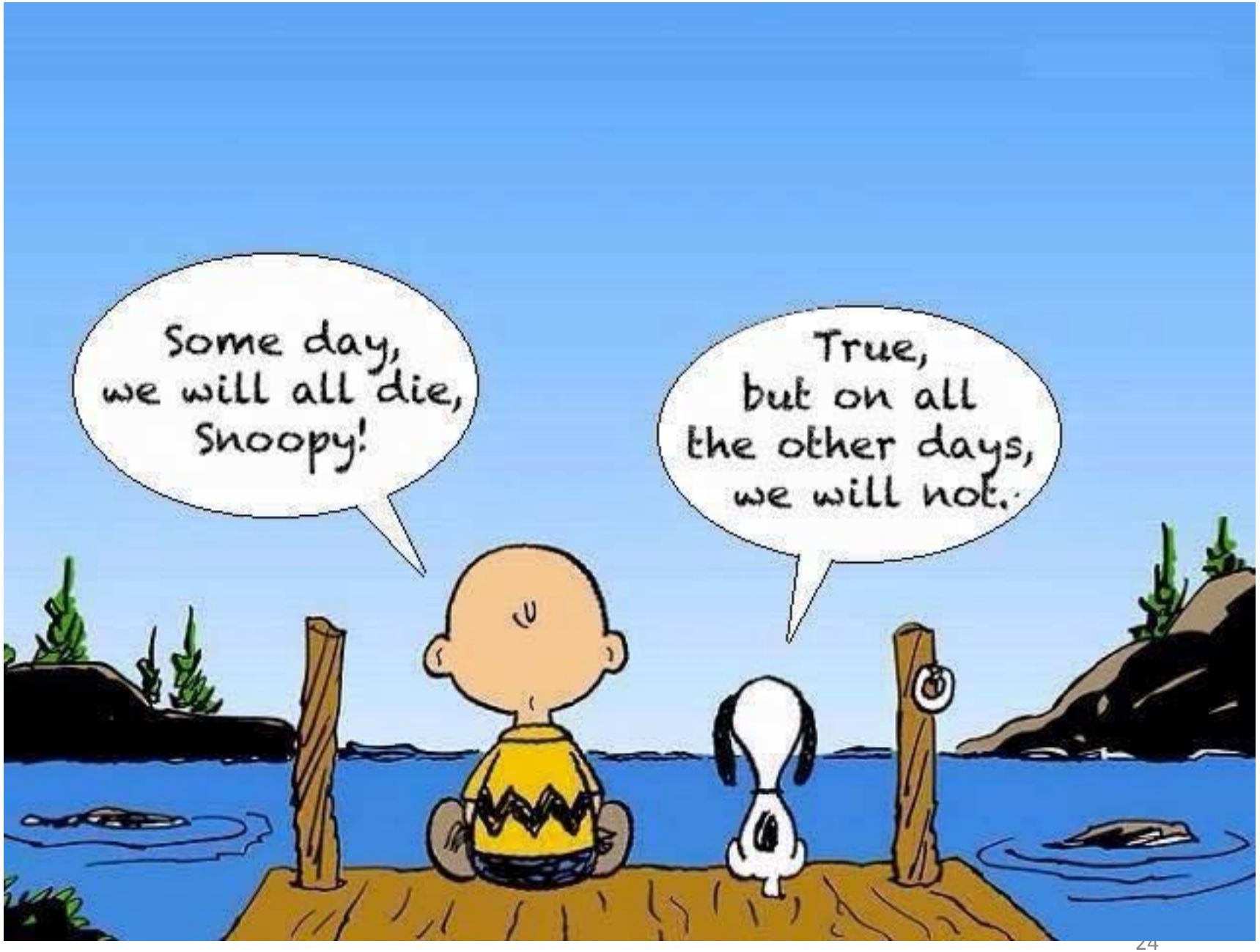
Olipudase - ERT



McGovern, M.M., Avetisyan, R., Sanson, BJ. *et al.* Disease manifestations and burden of illness in patients with acid sphingomyelinase deficiency (ASMD). *Orphanet J Rare Dis* **12**, 41 (2017). https://doi.org/10.1186/s13023-017-0572-x

Many LSDs have IV enzyme replacement therapies.

- Usually every 1-2 weeks for life.
- All have risk of infusion reactions similar to antibody therapies commonly used in oncology and treated similarly.
- If you are interested in being a site for providing infusion services please let us know.


Some day, we will all die, Snoopy!
True, but on all the other days, we will not.