IEMs for hematologists:

Porphyria and Gaucher disease

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Female, 21 years

2012-2015: 12 admissions in Emergency dept, 3 gastroscopies, two colonoscopies, 16 adominal imaging exams (3 CTs), 21 lab workups

→ Referral to liaison psychiatry

Seeks second opinion in university hospital

Admission Leuven

Abdominal pain for 1 week, nausea and vomiting
No inflammation, no peritonitis on physical exam, normal lactate
Repetitive imaging negative but distended colon with constipation

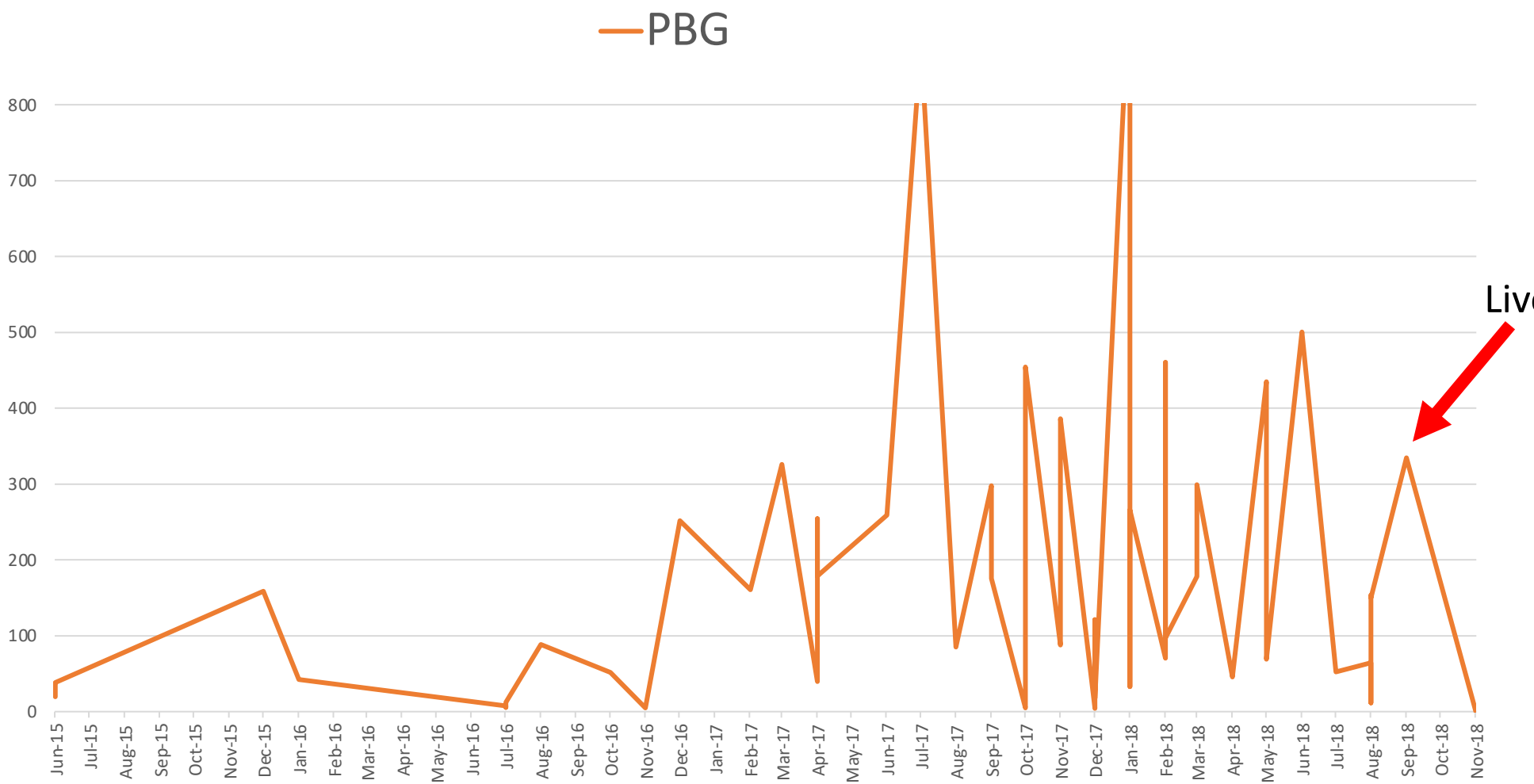
Hyponatremia 123 mmol/L (135-145)
pOsm 256 (low)
UNa 98 (too high)
UOsm 513 (too high)

→ “SIADH”

Lead, C1 esterase and porphyrins were checked

Spot urine			
PBG	*	38.4 mg/L	0.0 - 2.0
Blood			
PBG-deaminase	*	5.7 nmol/L RBC.s	6.8 - 14.3

Evolution next 3 years: attacks every 2wks

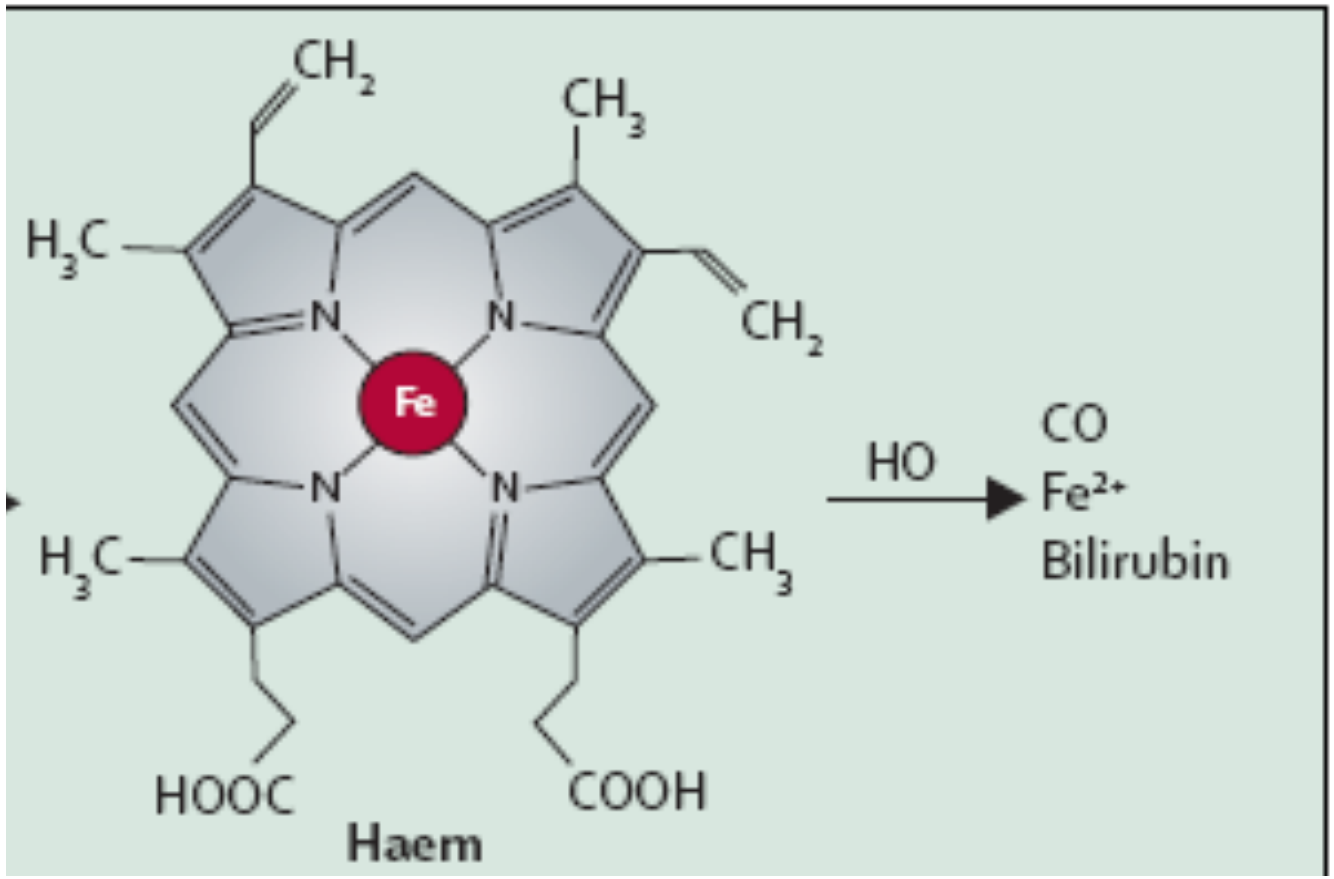


Liver transplantation

PBG < 2.0
ALA 1.0-5.7

Porphyrins are the substances that make plants green and blood red.

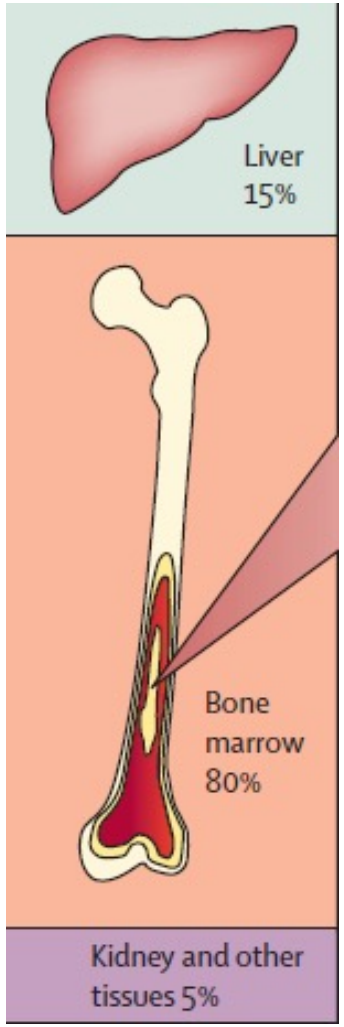
(Hans Fischer 1930)



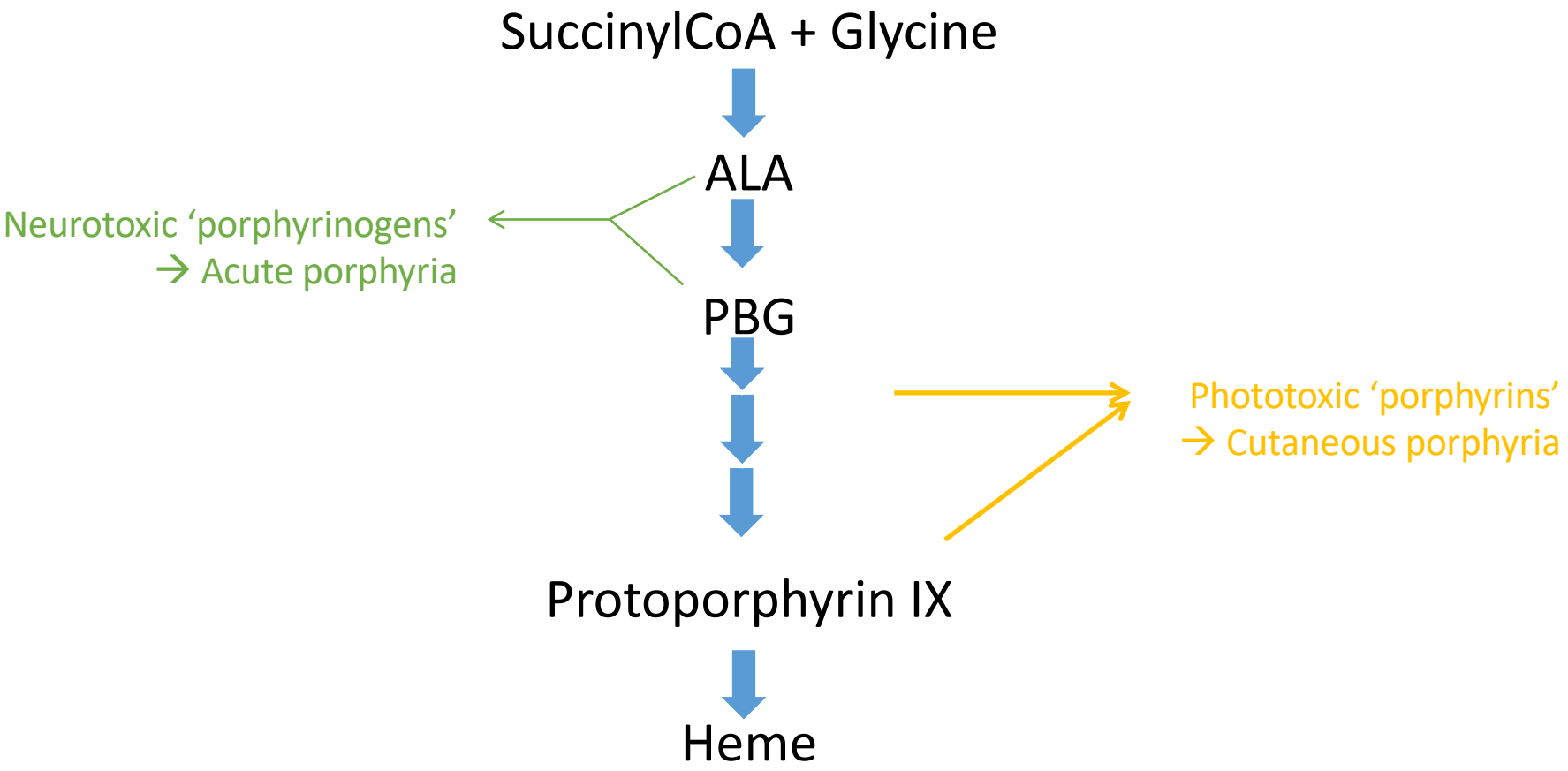
Haem

Heme

- Synthesized in every cell
- 80% in bone marrow (hemoglobin)
- 15% in liver: cytochrome P450 (CYP)
- Other heme-containing proteins:
  myoglobin, respiratory chain cytochromes, catalase, NO-synthase

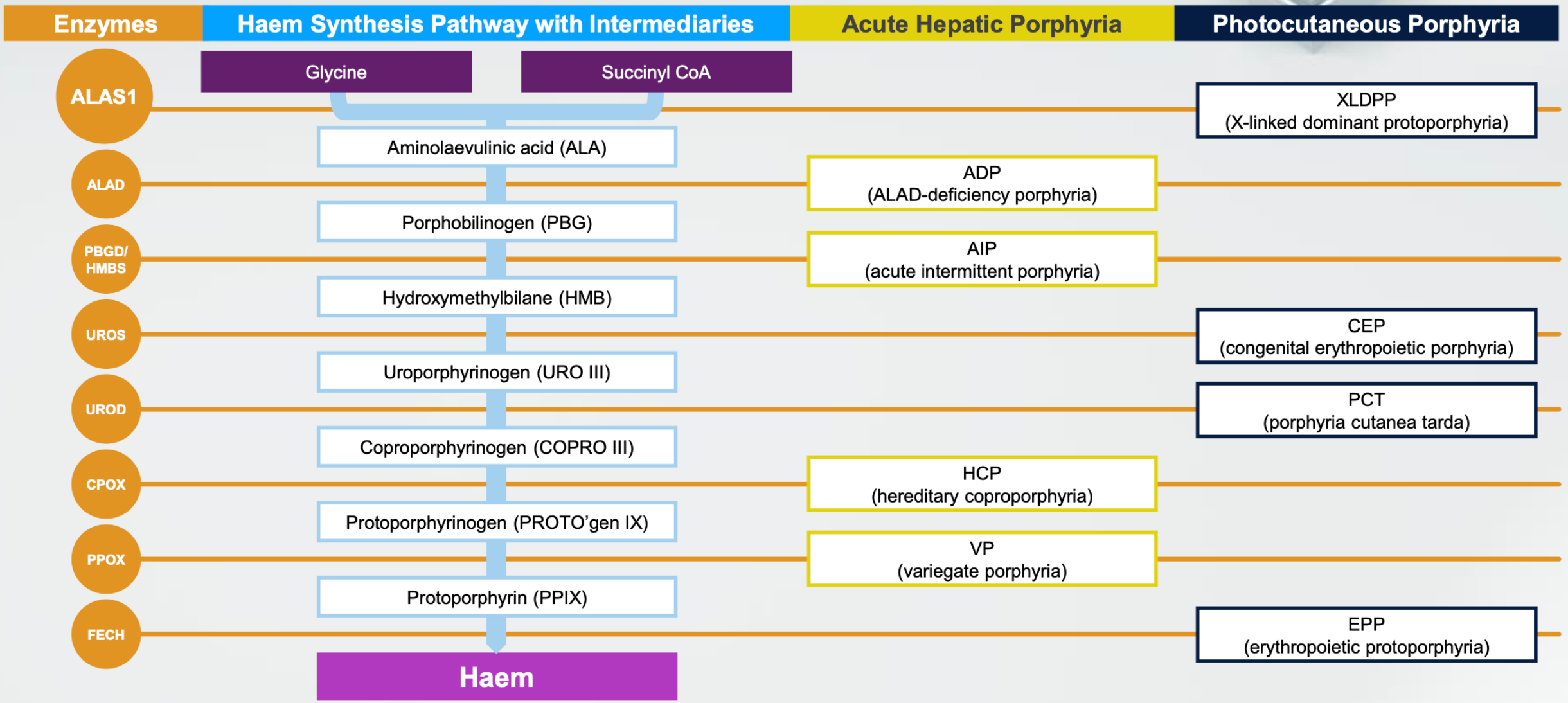


Heme synthesis



Haem Biosynthesis Pathway, Defective Enzymes, and Related Porphyria[1]

The Rate-Limiting Step for the Pathway is the Formation of ALA, Catalysed by ALAS1[2]



1. Bissell DM et al. *N Engl J Med.* 2017;377:862-872. **2.** Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26.

Most frequent porphyrias

- Cutaneous:
  - Blistering: PCT
  - Burning: EPP
- Acute: AIP

UZ Leuven: 50 PCT, 80 EPP, 50 acute

Estimated Prevalence of Most Common Types of Porphyria[1,4]

Type of Porphyria	Estimated Prevalence Based on European and US Data
Porphyria cutanea tarda (PCT)	1/10,000 (EU)[1]
Acute intermittent porphyria (AIP)	0.118-1/20,000 (EU)[1,4] 5/100,000 (US)[1]
Erythropoietic protoporphyria (EPP)	1/50,000-75,000 (EU)[1]

1. Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet*. 2015;86:1-26. **2.** Puy H et al. *Lancet.* 2010;375:924-937. **3.** Bissell DM et al. *N Engl J Med.* 2017;377:862-872. **4.** Elder G et al. *J Inherit Metab Dis*. 2013;36:848-857.

Porphyrias are genetic diseases (+/-)

- Autosomal dominant
- LOW PENETRANCE: 1% in the wild, 10% within families with symptomatic proband

AHP: 1 variant carrier out of 1700 (?),

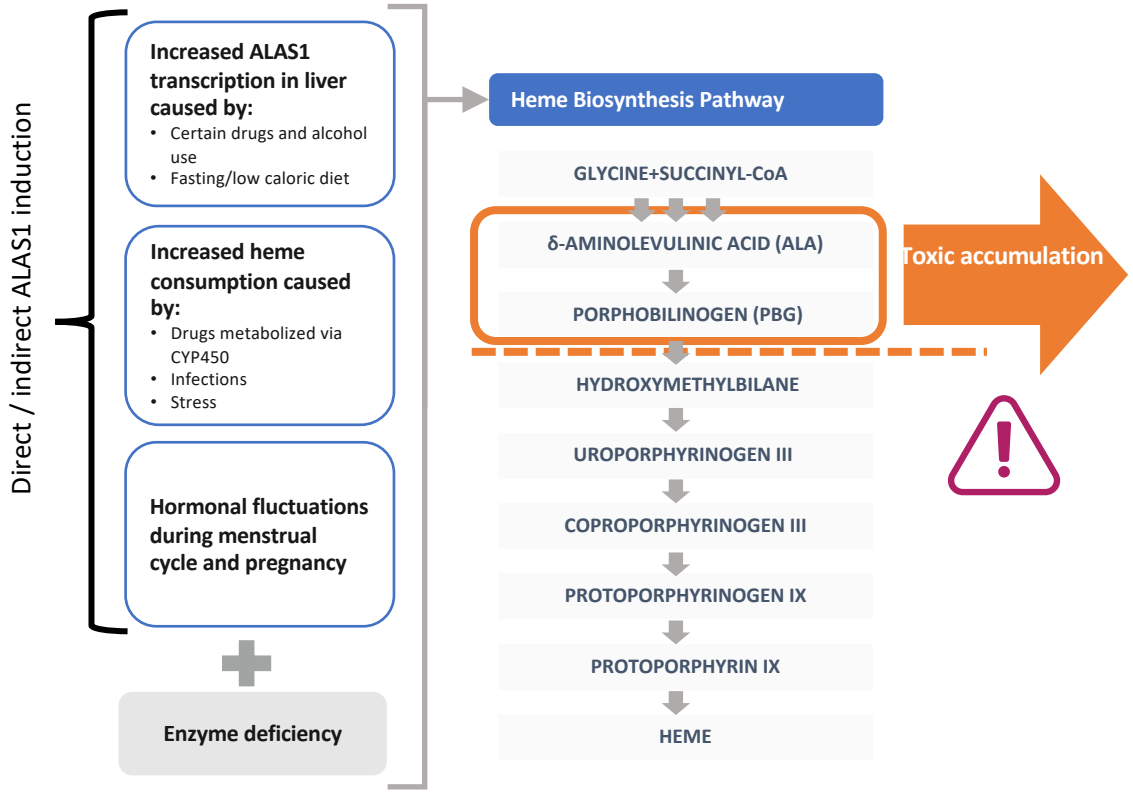
1 symptomatic person (female:male = 5:1) out of 170.000 (?)

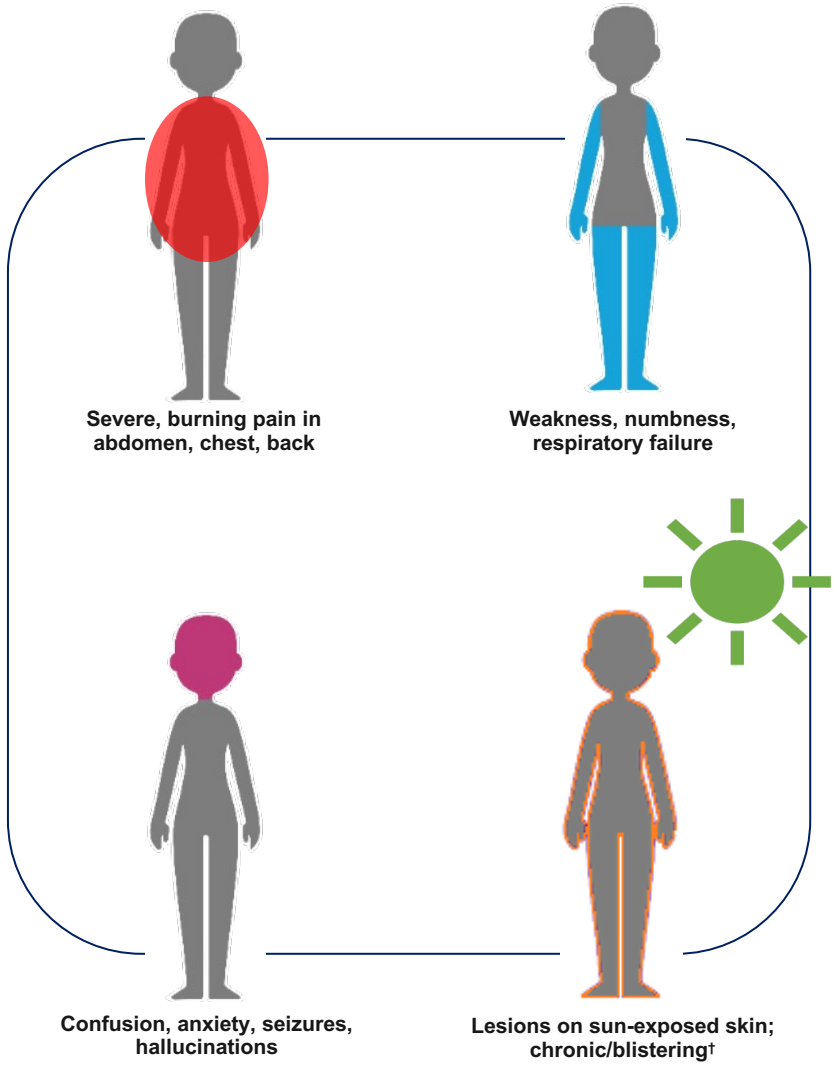
PCT: 80% acquired (any liver disease), 20% genetic (AD)

EPP: pseudo-dominant and small minority X-linked

Acute (Hepatic) Porphyria (AP)

Pathophysiology



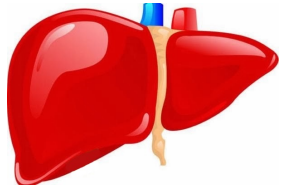


† Only occurs in Variegate porphyria and Hereditary coproporphyria

1. Anderson KE et al. Ann Intern Med. 2005;142:439-450; 2. Ventura P et al. Eur J Intern Med. 2014;25:497-505; 3. Bonkovsky HL et al. AASLD 2018. Poster; 4. Besur S et al. Metabolites.2014;4:977-1006; 5. Pischik E, Kauppinen R. Appl Clin Genet. 2015;8:201-214; 6. Szlendak U et al. Adv Clin Exp Med. 2016;25:361-368; 7. Bissell DM et al. N Engl J Med. 2017;377:862-872.

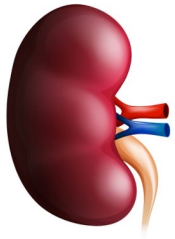
Long-term Complications of AHP

Liver and Kidney Disease in AHP

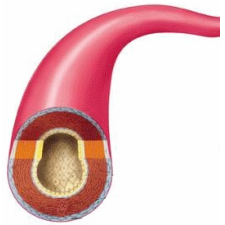


- hepatocellular carcinoma[1]
  - annual incidence 0.35% or 108-fold higher than reference population[2]

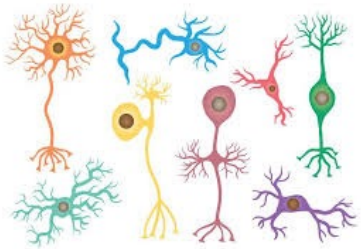
US surveillance /6mo after age 50!!



- chronic kidney disease
  - 30%–60% of patients with symptomatic AHP[4,5]



- chronic sustained hypertension[3,6]



- Axonal motor polyneuropathy → pain[7]
- Permanent quadriplegia [8]

1. Peoc'h et al. *Mol Genet Metab.* 2018;S1096-7192(18):30482-30487. 2. Baravelli CM et al. *J Intern Med.* 2017;282:229-240. 3. Pallet N et al. *Clin Kidney J.* 2018;11:191-197. 4. Pallet N et al. *Kidney Int.* 2015;88:386-395. 5. Alnylam. Data on file (EXPLORE dataset). 6. Stewart MF. *J Clin Pathol.* 2012;65:976-980. 7. Wang B. *Hepatology Communications*. 2019;3(2):193-206. 8. Wikberg et al. Lakartidningen. 2001 Sep 19;98(38):4038-41

First line screening for AP

- Accuracy and speed are vital
- Delaying treatment can lead to neurologic damage and possibly death[2]

1st Line Biochemical Testing[1-3]

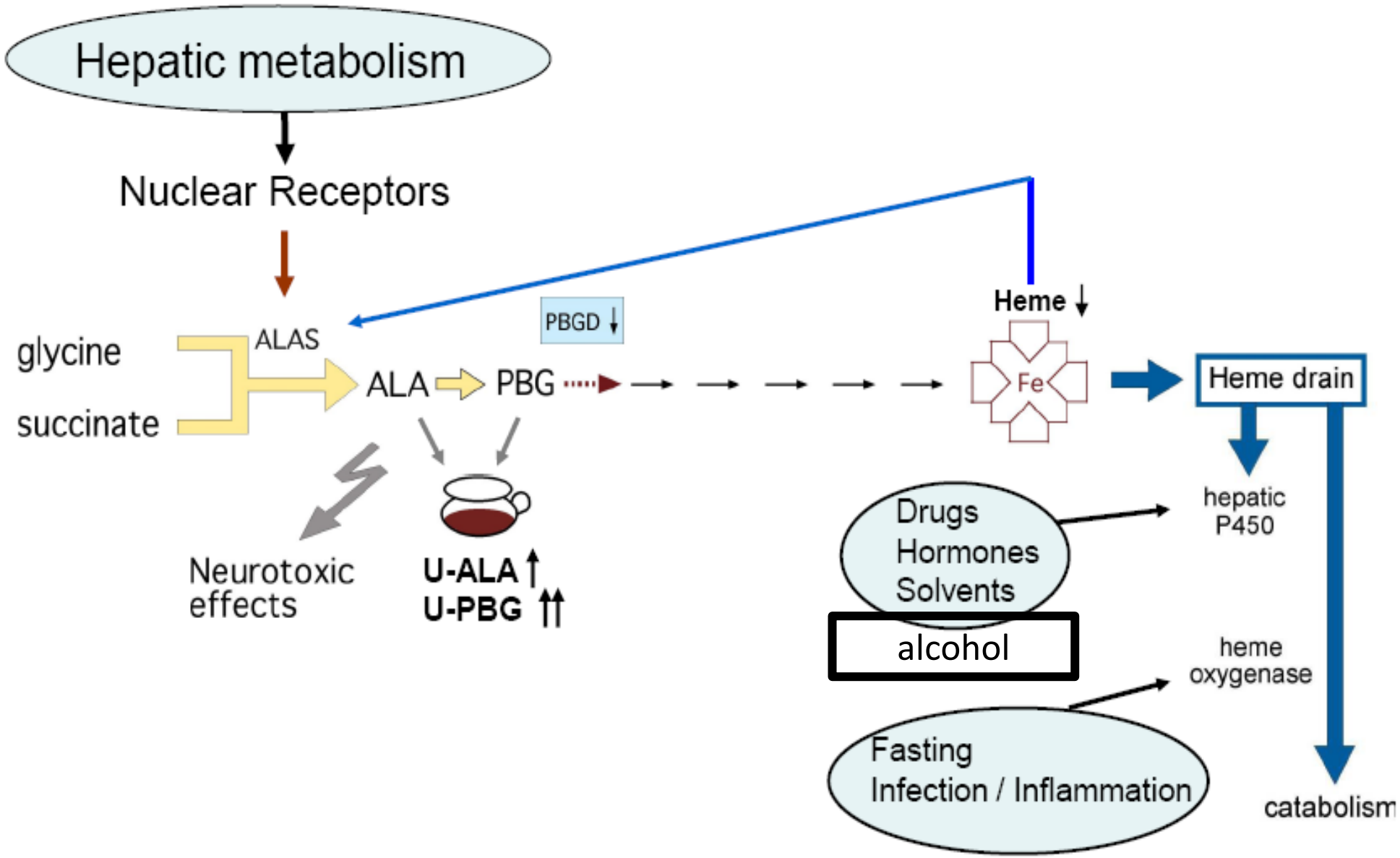
- Random **(spot) urine** test for ALA and **PBG**[†]
- Ideal time: during or days after a suspected attack

Additional Testing[1-3]

- Plasma or fecal porphyrins
- Genetic testing!!

[†]Porphyrins should not be tested alone without ALA or PBG.

1. Bonkovsky HL, et al. *Am J Med*. 2014;127:1233-41. 2. Anderson KE et al. *Ann Intern Med* 2005;142:439–450. 3. Whatley SD, Badminton MN. Acute Intermittent Porphyria. In: GeneReviews. Seattle, WA: University of Washington, Seattle; Updated 2013.


Hepatic metabolism
Nuclear Receptors
glycine
succinate
ALAS
ALA
PBG
PBGD
Heme
Fe
Heme drain
Neurotoxic effects
U-ALA
U-PBG
Drugs
Hormones
Solvents
alcohol
hepatic P450
heme oxygenase
Fasting
Infection / Inflammation
catabolism

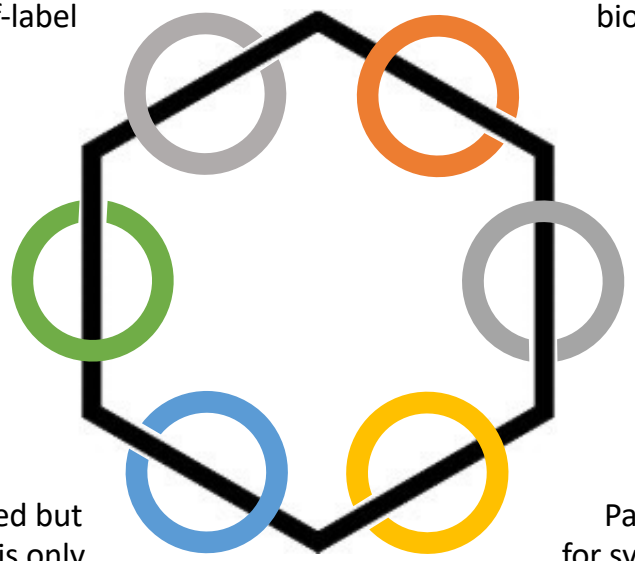
Current Treatment Approaches for AP

Elimination of disease triggers! Alcohol, meds, smoking, fasting, infections

Hemin[1]
is approved for the treatment of acute attacks and used prophylactically off-label

Pain medications[1]
Patients with AHP are commonly prescribed opioid pain medications

Liver Transplantation[1]
Liver transplantation is rarely used but due to associated complications is only suitable for severely affected patients



Glucose and carbohydrate loading[1]
May downregulate the heme biosynthesis pathway and shorten the length of an attack

Hormone therapy[1]
GnRH agonists may be used chronically for females experiencing an acute attack related to their menstrual cycles

Treatment of AHP symptoms[1]
Patients with AHP often receive medications for symptoms including but not limited to, nausea, hypertensive crises, neuropathy, seizures, metabolic changes, anxiety and depression

1. Wang. Acute Hepatic Porphyrias: Review and Recent Progress. Hepatol Commun. 2018 Dec 20;3(2):193-206.

Treatment Acute (Hepatic) Porphyria

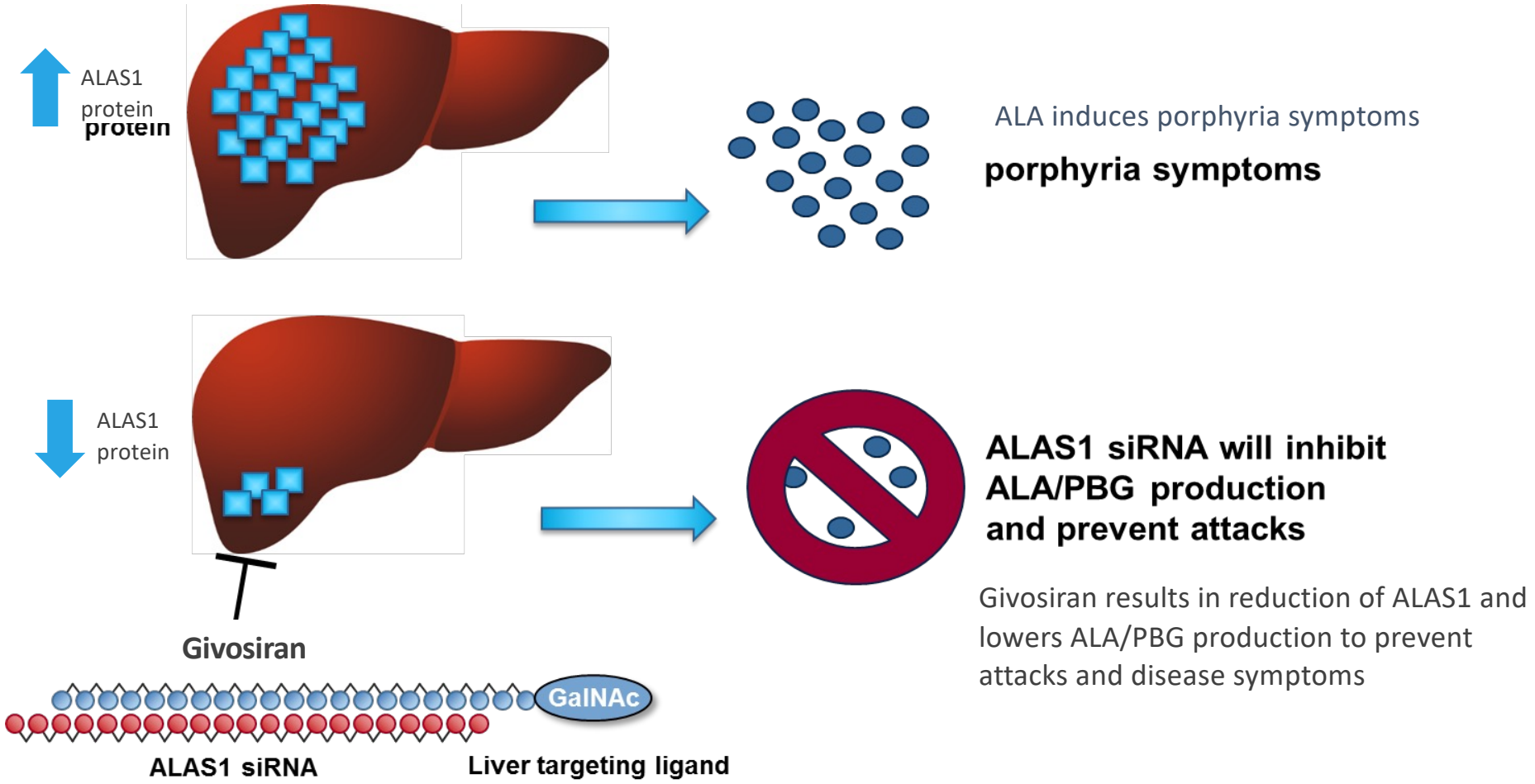
- Supportive (glucose 3L 10%, opiates, anti-emetics)
- ONLY SAFE MEDS www.porphyria-europe.com
- ? Removal/avoidance of precipitating factor
- IV hemin for attack: Normosang1 flask/d, 4 days (cave thrombosis → DVC!)
- Givosiran RNAi 1/month for recurrent attacks (“prevention”)

→ Liver Tx as an option for patients with recurrent attacks

Prognosis is excellent if diagnosed early

Givosiran (Givlaari®): ALAS1 RNAi

Reduction of Liver ALAS1 Protein to Lower ALA and PBG



Givosiran results in reduction of ALAS1 and lowers ALA/PBG production to prevent attacks and disease symptoms

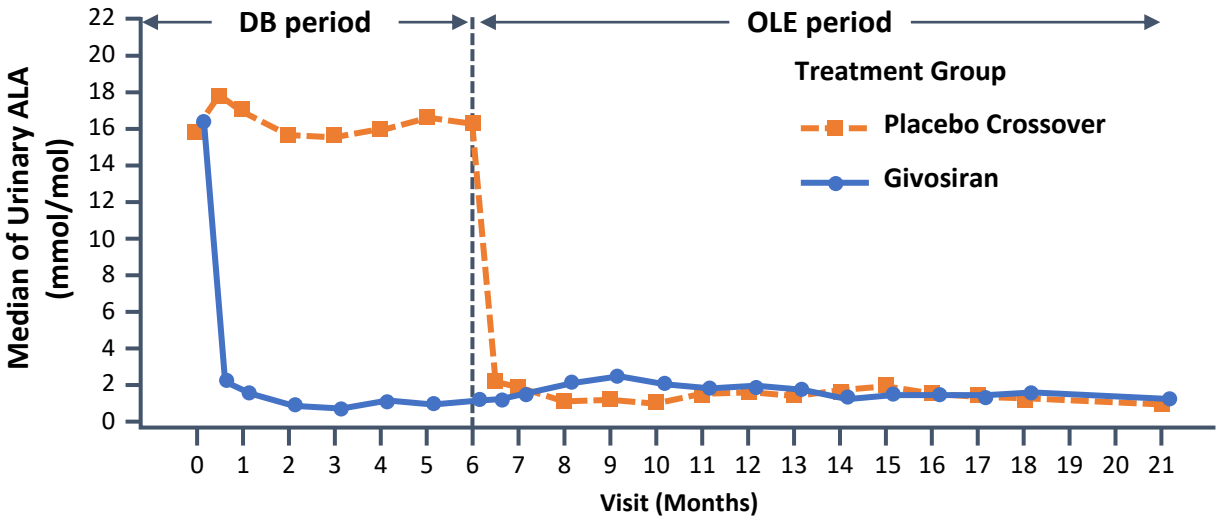
AHP, Acute Hepatic Porphyria; ALA, Aminolevulinic acid; ALAS1, ALA synthase 1; PBG, Porphobilinogen.

Balwani et al. – "ENVISION, a Phase 3 Study to Evaluate the Efficacy and Safety of Givosiran, an Investigational RNAi Therapeutic Targeting Aminolevulinic Acid Synthase 1, in Acute Hepatic Porphyria Patients" - EASL 2019

Sustained Lowering of ALA and PBG Levels with Long-Term Dosing

- During the OLE, givosiran treatment led to sustained reductions in ALA and PBG levels through Month 18
- Patients with AHP achieved near normalization or normalization of ALA and PBG levels with givosiran treatment[1]

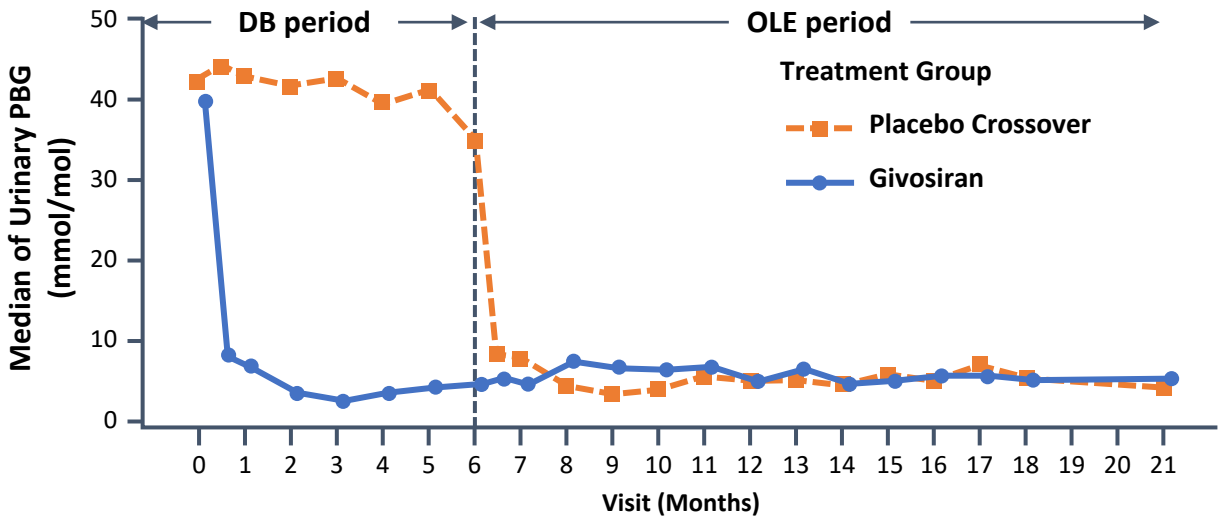
Median Urinary ALA Levels over Time[a]



No. of patients:

PBO/Givo	46	42	44	42	46	39	45	41	44	45	44	42	43	43	41	42	40	41	41	40	39	19
Givo/Givo	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	44	43	44	46	45	45	19

Median Urinary PBG Levels over Time[a]



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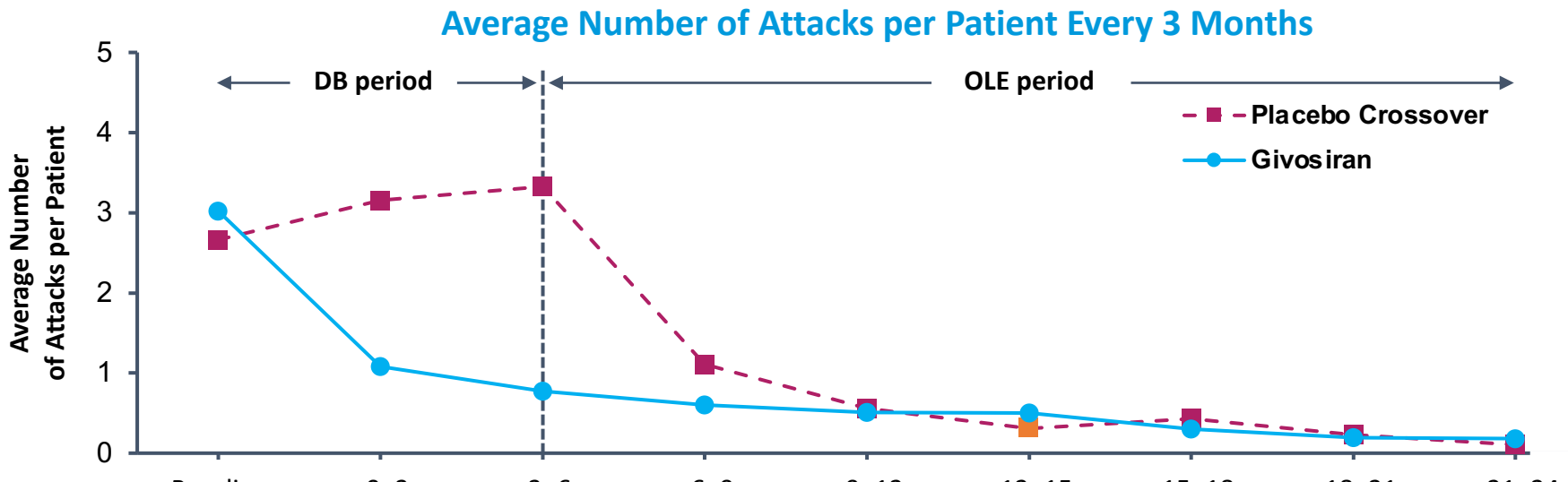
Givo/Givo	48	47	47	48	47	45	44	46	43	44	46	46	45	45	45	44	43	44	46	45	45	19

[a]OLE data for givosiran 1.25 mg/kg and 2.5 mg/kg groups are pooled

AHP, acute hepatic porphyria; ALA, δ-aminolevulinic acid; DB, double-blind; Givo, givosiran; OLE, open-label extension; PBG, porphobilinogen; PBO, placebo

1. Agarwal et al. *JIMD Reports* 2020; DOI:10.1002/jmd2.12173

Long-Term Givosiran Dosing Led to Sustained Reduction of Attacks



No. of patients									
Placebo crossover	46	46	46	46	45	45	44	43	19
Givosiran	48	48	48	48	47	46	46	46	22

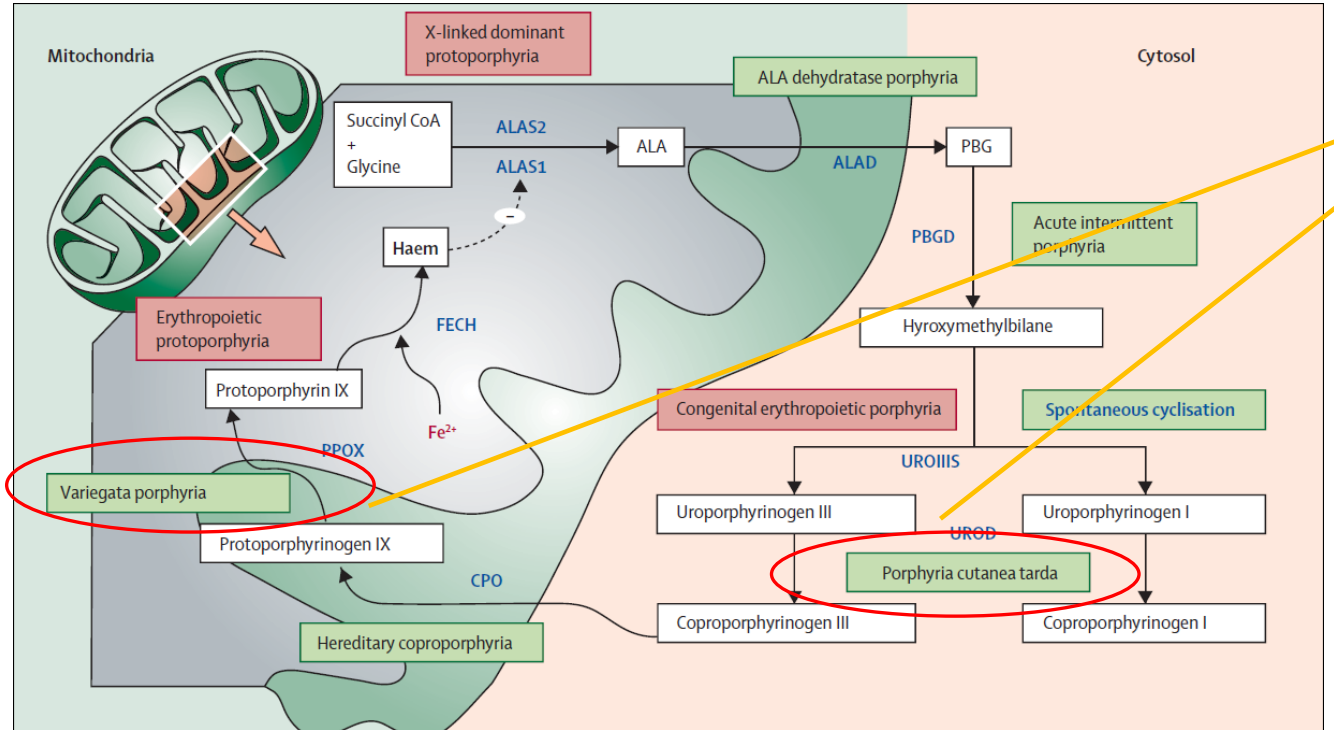
- With a further 6 months of givosiran treatment, proportion of patients with zero attacks during the OLE period was sustained
  - 61.7% vs 60.9% (Month 12 vs Month 18) for continued givosiran patients[1]
  - 42.2% vs 40.0% (Month 12 vs Month 18) for placebo crossover patients[1]

[a]The estimate for each 3-month interval is calculated as total number of attacks/total number of patients reached that 3 months. Three months=28 × 3 days. [b]OLE data for 1.25 mg/kg and 2.5 mg/kg are pooled

DB, double-blind; OLE, open-label extension

1. Sardh et al. Presented at *The Digital International Liver Congress* 2020. Oral

Cutaneous BLISTERING porphyrias



Porphyrins that build up in the skin

↓

UV light

↓

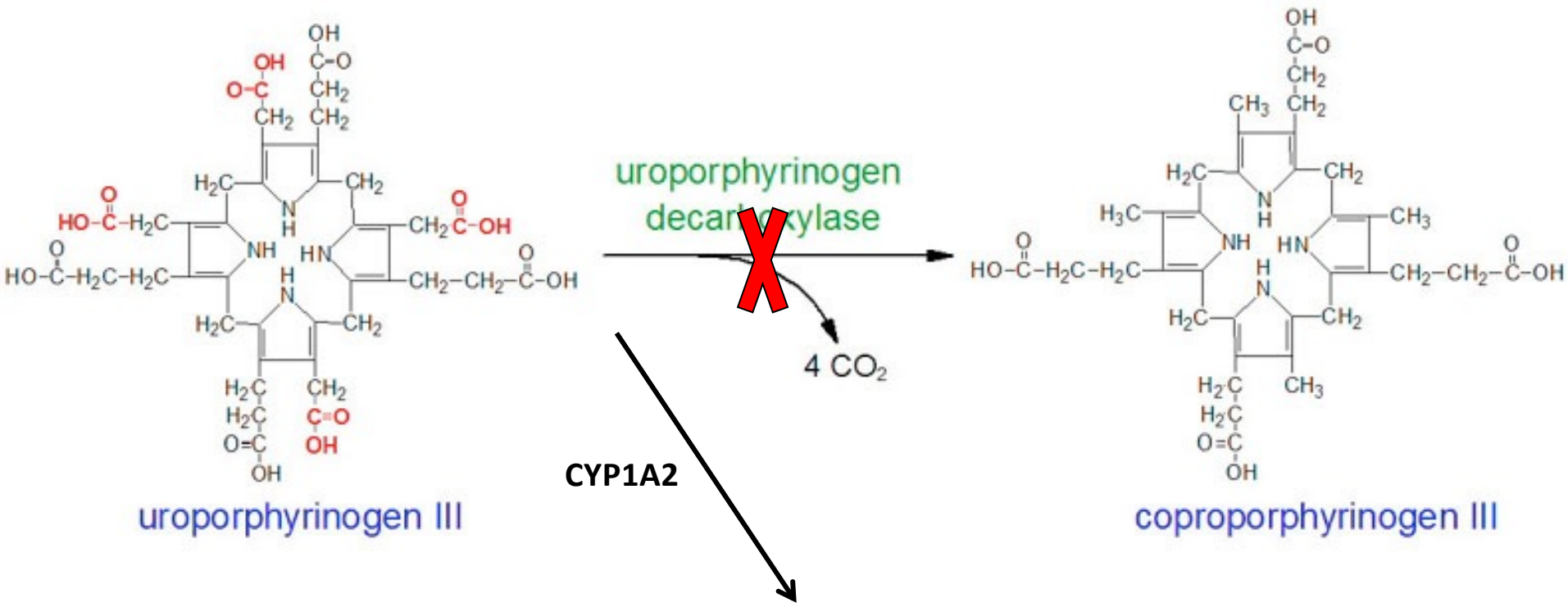
Excitation and oxidative stress

↓

Blisters

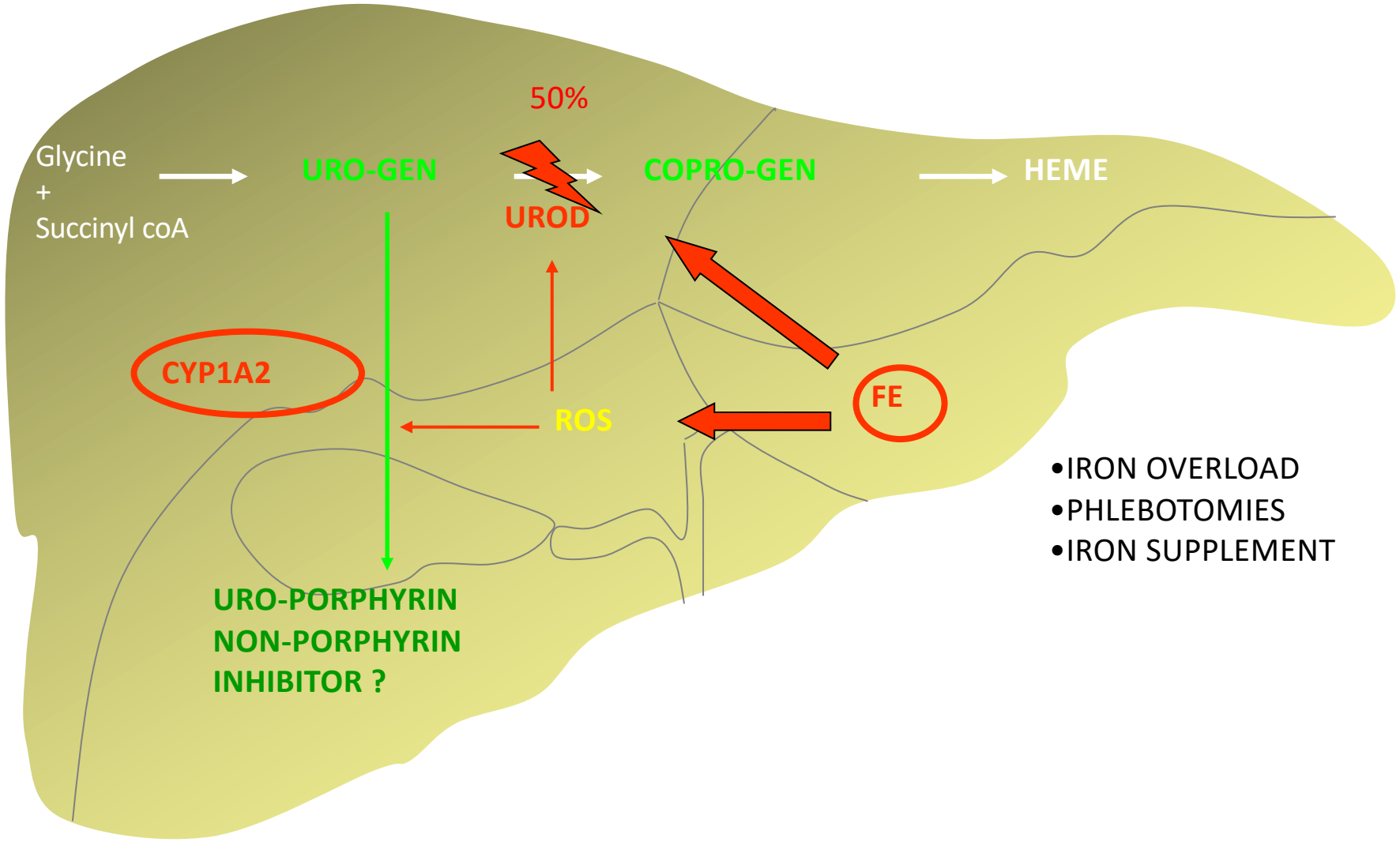
Porphyria cutanea tarda (PCT)

- By far most frequent porphyria (1/5.000-25.000)
- 20% familial
  - Autosomal dominant with low penetrance
- **80% sporadic**, acquired
  - No mutation, acquired inhibition of UROD
  - Men > women



Penta- Hexa- Heptacarboxylporfyrine

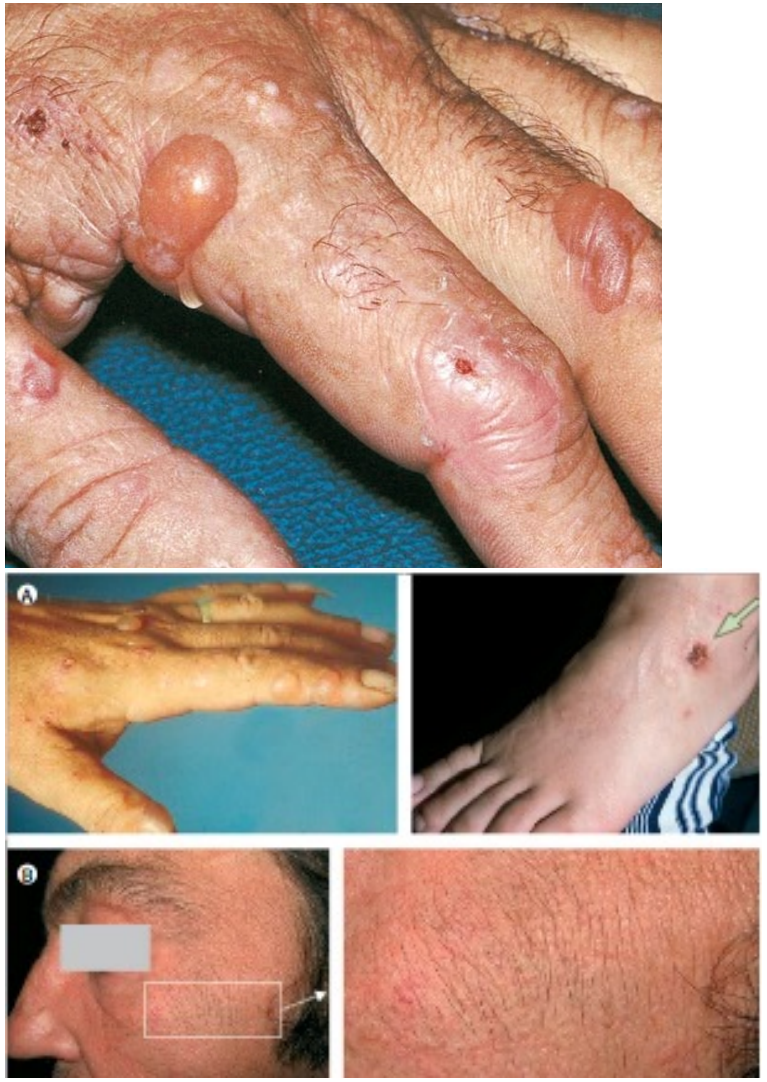
PCT: can occur with ANY chronic liver disease



- IRON OVERLOAD
- PHLEBOTOMIES
- IRON SUPPLEMENT

Clinical presentation

- Blisters in sun-exposed areas
- Fragile skin
- Hyperpigmentation
- Milia (small white inclusions)
- Hypertrichosis
- Liver function abnormalities
  - In association with alcohol, iron
  - Cirrhosis and HCC

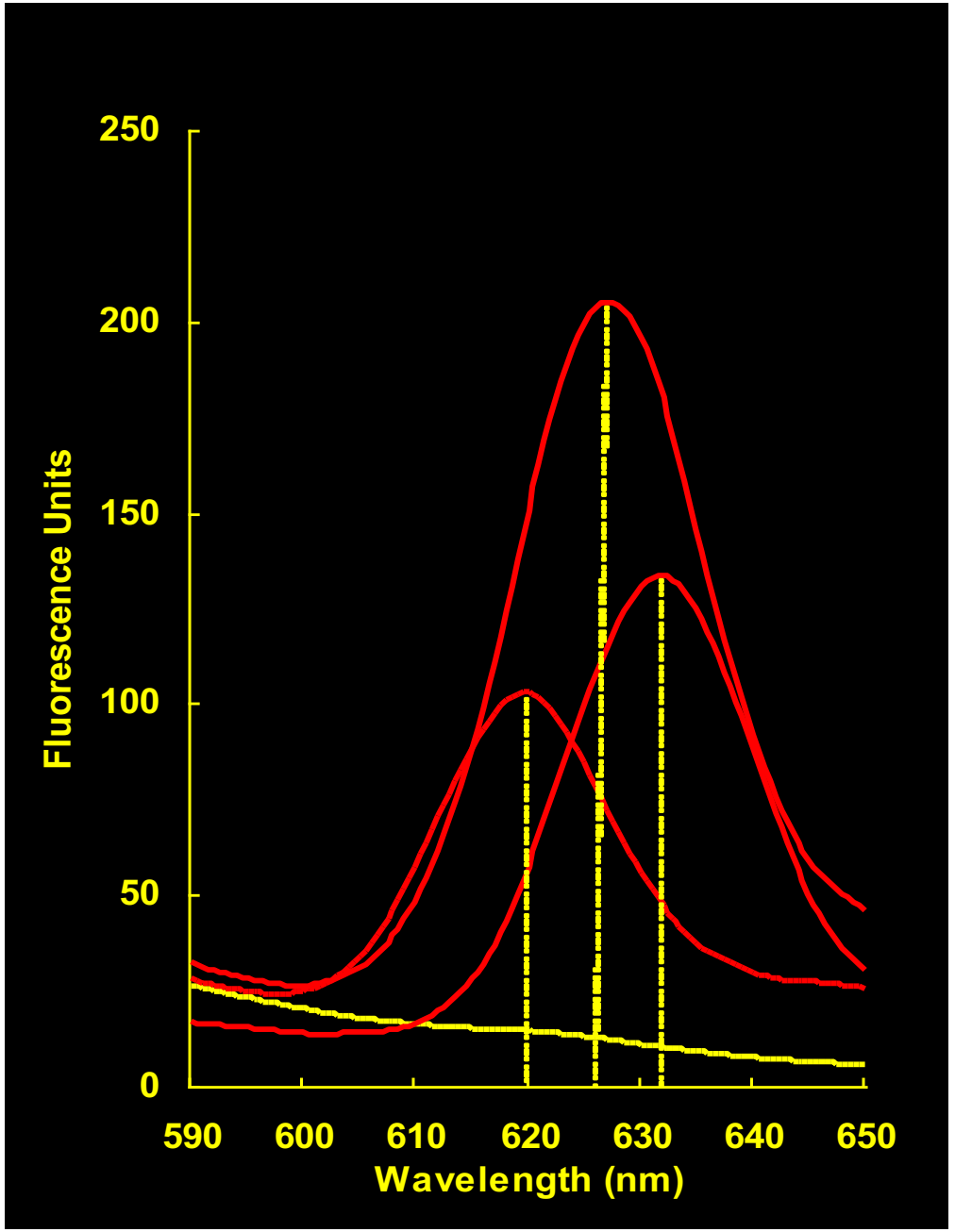


Diagnosis

- Plasma scan
  - VP: peak at 624-628 nm
  - PCT: peak 620 nm
- Further differentiation: urinary porphyrins
  - PCT: **heptacarboxyl porphyrin**
- (genetics in familial or unexplained cases)

Plasma Peak	Porphyria
615-620 nm	PCT
624-627 nm	VP
626-634 nm	EPP

Negative = no active cutaneous porphyria



Treatment

- Protection from sunlight
- Avoid precipitating factors (alcohol, smoking, ...)
- <u>In PCT:</u>
  - *Chloroquine* 150 mg 2x/week
    - Complexes with porphyrins → excretion in urine
  - *Phlebotomy*
    - 300-500 cc weekly until ferritin < 100ug/L

BURNING cutaneous porphyria

- Erythropoietic protoporphyria (EPP) = 90%
  - Ferrochelatase deficiency
  - Inherited
    - Pseudodominant:
      - 1 mutant allel (no activity) – 1 polymorphous allele with reduced activity (10% of the population)
    - Homo- or compound heterozygote: severe disease with liver involvement
  - Acquired
    - Myelodysplasia and myeloproliferative disorders
- X-linked dominant protoporphyria (XLDPP) = 10%
  - Men > women
  - Increased ALAS2 activity
  - Gain of function mutation

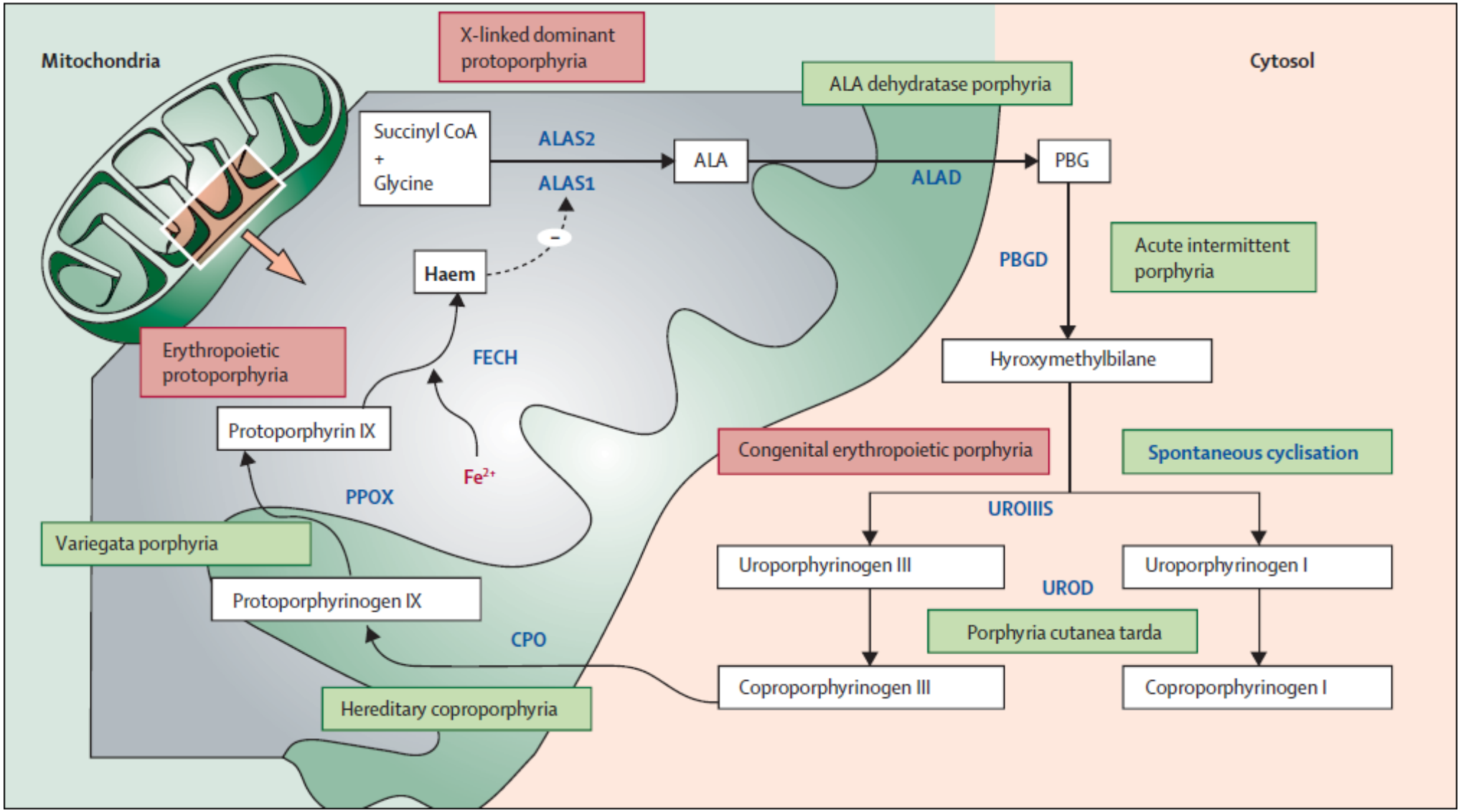


Figure 1: **Haem biosynthetic pathway and porphyrias**

Green boxes=hepatic porphyrias. Red boxes=errythropoietic porphyrias. ALA=5-aminolaevulinic acid. PBG=porphobilinogen. I, III, or IX=type isomers. ALAS=ALA-synthase. ALAD=ALA-dehydratase. PBGD=porphobilinogen deaminase. UROIIIS=uroporphyrinogen III synthase. UROD=uroporphyrinogen decarboxylase. CPO=coproporphyrinogen oxidase. PPOX=protoporphyrinogen oxidase. FECH=ferrochelatase. Fe^{2+}=ferrous iron.

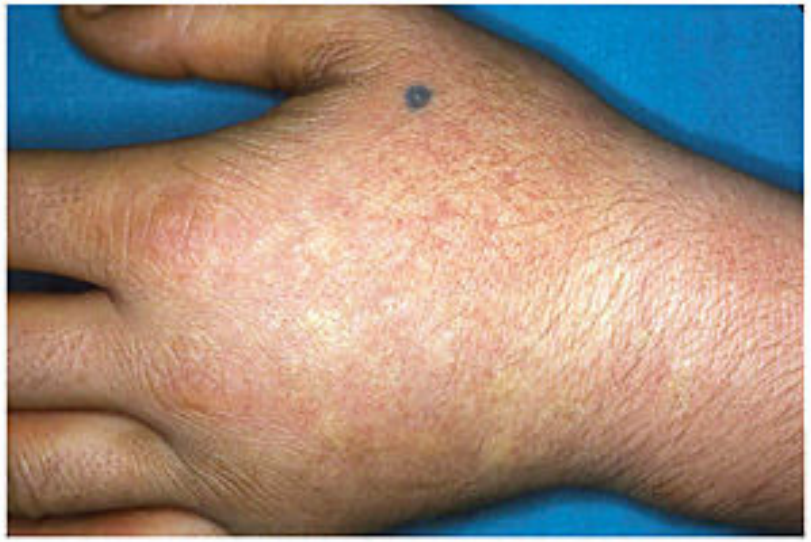
Clinical presentation

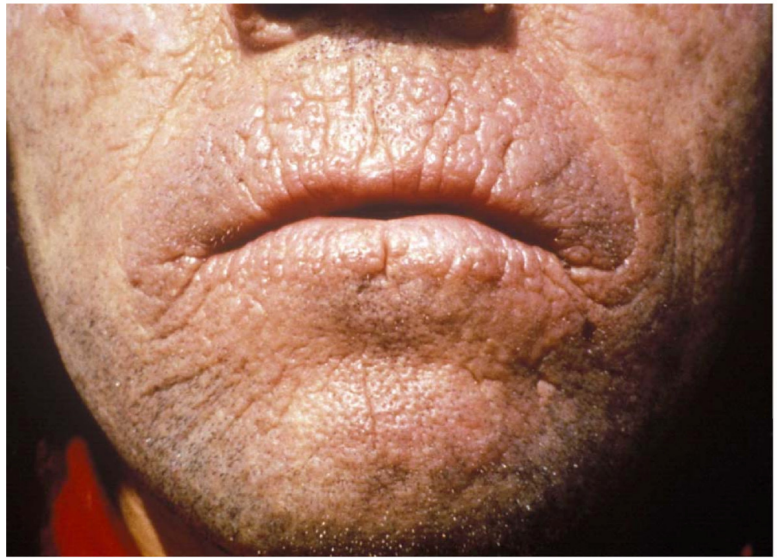
Acute photosensitivity

- From childhood!
- Burning painful sensation after a few minutes of sun exposure
- Edema and erythema
- Skin tighter
- Scars and wrinkles in the face

Liver abnormalities (in 10-20%)

Protoporphyrin bile plugs and stones in bile canaliculi ➔ Cholestatic liver failure in 2%





Diagnosis EPP

Protoporphyrin is lipid soluble → no urinary excretion

- Free Erythrocyte Protoporphyrin: FEP test
- Plasma scan: peak at 634 nm
- FECH and ALAS2 genetics

Treatment EPP

- Protection from the sun: sun screens with metallic filter
- UVB phototherapy
- Afamelanotide (alfa-MSH, Scenesse) → melanin formation
- Beta-carotene (75-200 mg/day)
- In case of liver abnormalities
  - UDCA 3x250 mg (?)
  - Liver failure ➔ liverTx and HSCTx

Epnet is now transformed to Ipnet, the International Porphyria Network.

www.porphyrianet.org

Gaucher disease - A lysosomal storage disorder

- Most common **lysosomal storage disorder**[1]
- Progressive, heterogeneous, multi-systemic disease which can lead to debilitating and life-threatening complications[2,3]
- Autosomal recessive inheritance (chromosome 1)[1,4]
- Deficiency in **acid-β-glucosidase** (glucocerebrosidase) enzyme activity[3]
- Engorged macrophages (Gaucher cells) due to accumulation of glucosylceramide in the lysosomes of these cells[4]

1. Weinreb NJ. *Clinical Advances in Hematology and Oncology* 2012;10:3-6 **2.** Mistry PK, et al. *Am J Hematol* 2007;82:697–701. **3.** Mistry PK, et al. *Am J Hematol* 2011;86(1):110-115. **4.** Grabowski GA, Petsko GA, Kolodny EH. Gaucher Disease. In: Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A, Gibson K, Mitchell G. eds. New York, NY: McGraw-Hill; 2014. http://ommbid.mhmedical.com/content.aspx?bookid=971&Sectionid=62643884. Accessed August 03, 2015.

Bone marrow biopsy shows no sign of malignant process but some cells have a crinkled tissue-like appearance.

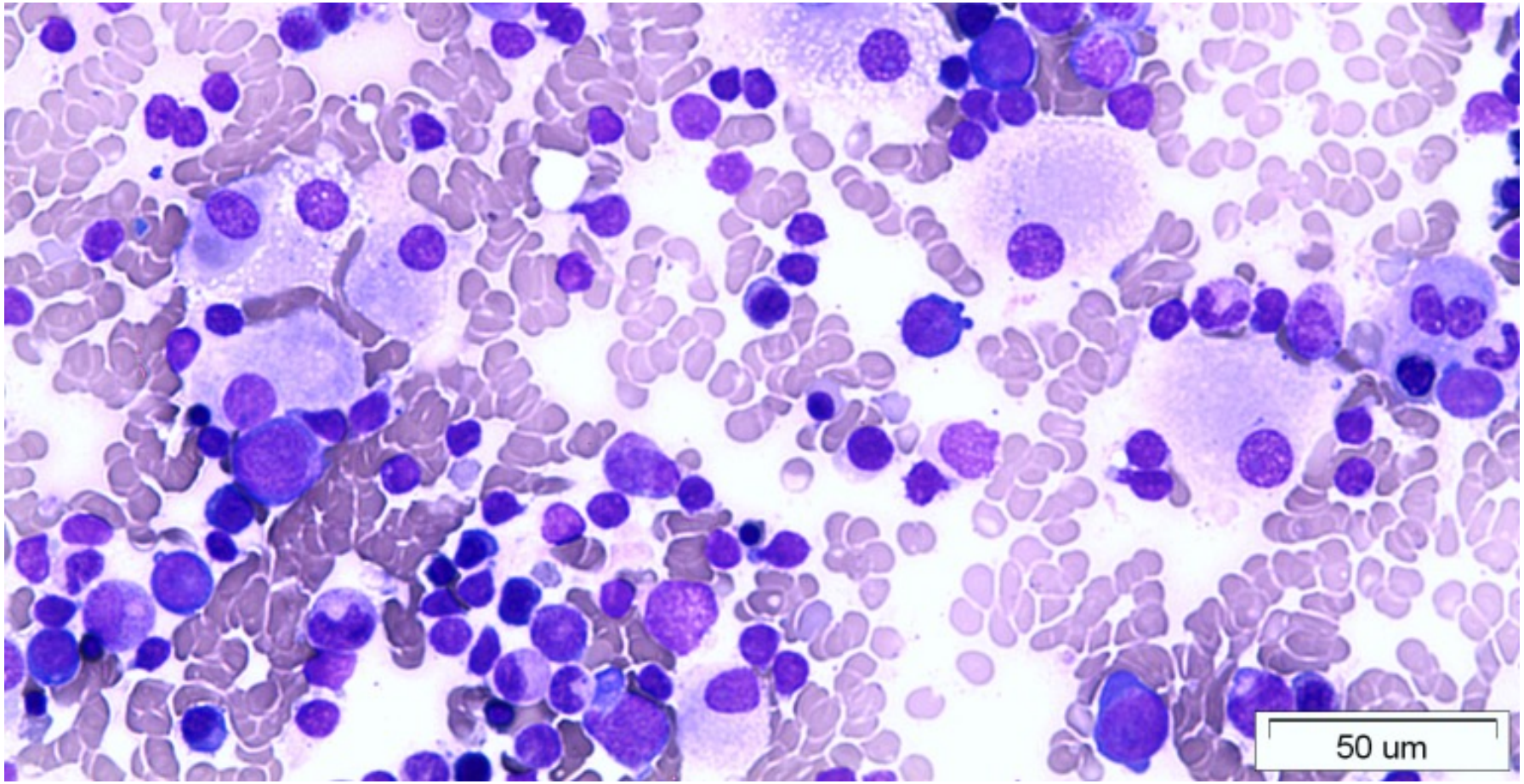
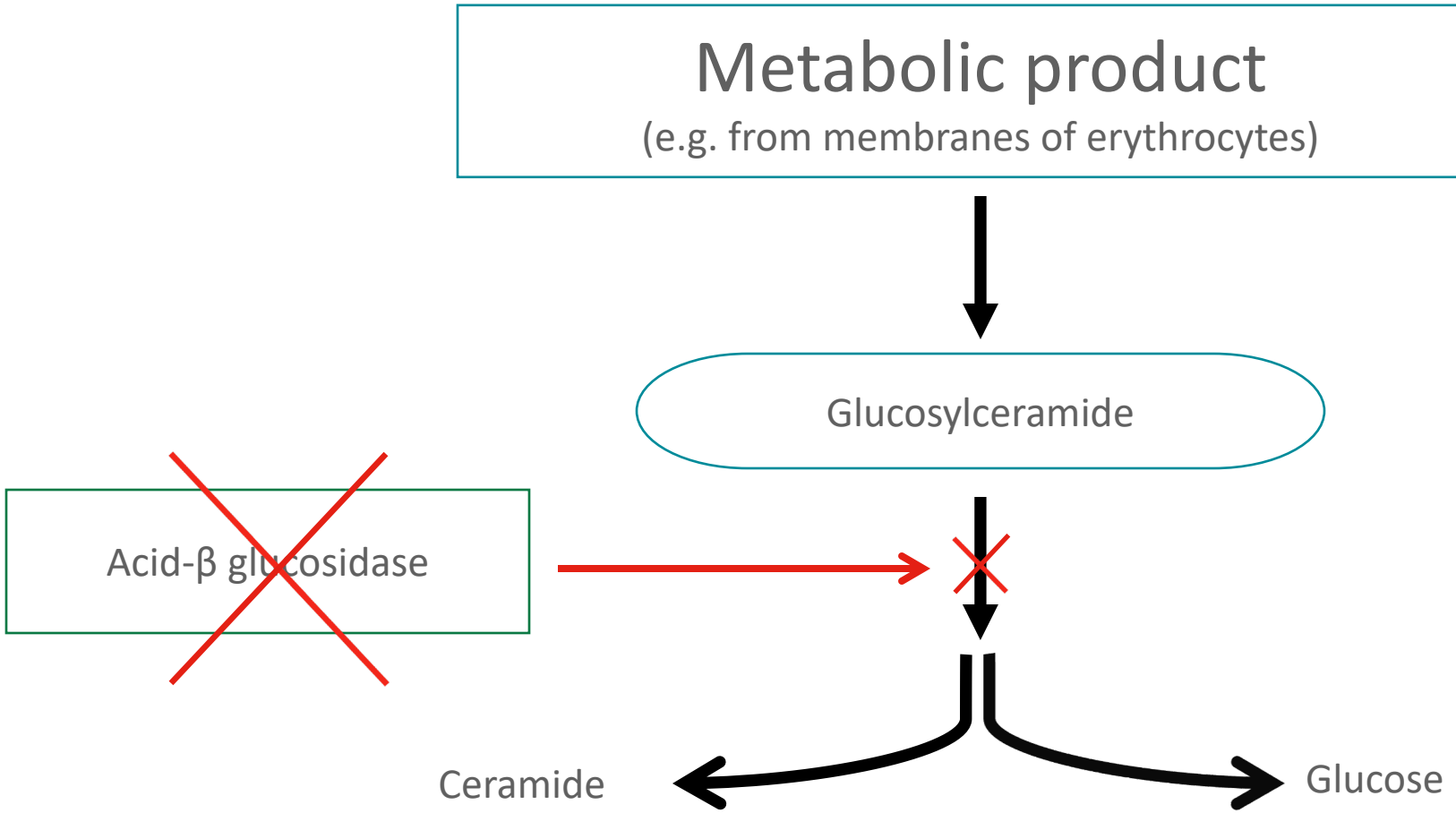


Image courtesy of Dr. T. Marinakis

Reduction in the activity of the enzyme acid-β glucosidase



Gaucher disease - Subtypes

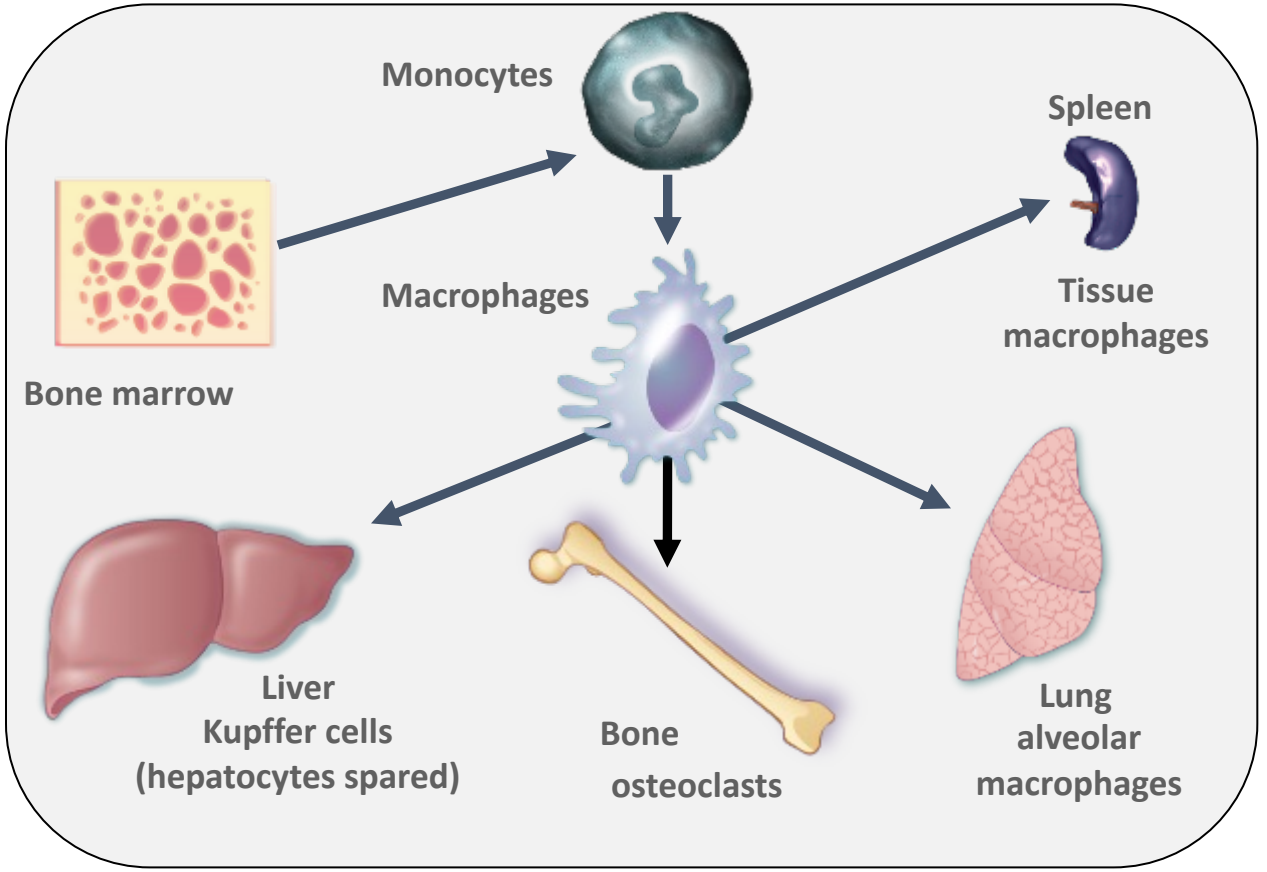
- Non-neuronopathic (type 1)
    - Prevalence of 1:50.000 to 1:100.000 worldwide
    - Prevalence in Ashkenazi Jewish population 1:850
    - Clinical manifestation possible at every age

- Neuronopathic (type 2 and type 3)
    - Acute (type 2): manifestation in the first year of life with a life expectancy up to 2 years[2]
    - Chronic (type 3): manifestation in early childhood[2]
    - Neuronopathic Gaucher disease has a prevalence of <1:100.000[3]

1. Mistry PK,et al. *Am J Hematol.* 2011;86(1):110-115 **2.** Grabowski GA, Petsko GA, Kolodny EH. Gaucher Disease. In: Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A, Gibson K, Mitchell G. eds. New York, NY: McGraw-Hill; 2014. http://ommbid.mhmedical.com/content.aspx?bookid=971&Sectionid=62643884. Accessed August 03, 2015. **3.** Davies E, et al. *JIMD* 2007 Oct30(5):935-42.

Glucosylceramide storing macrophages

- Bone marrow infiltration
- Cytopenia



- Massive splenomegaly
- Cytopenia
- Hypermetabolic state: fatigue

- Hepatomegaly
- Cirrhosis
- Portal hypertension
- HCC

- Infiltrative lung disease

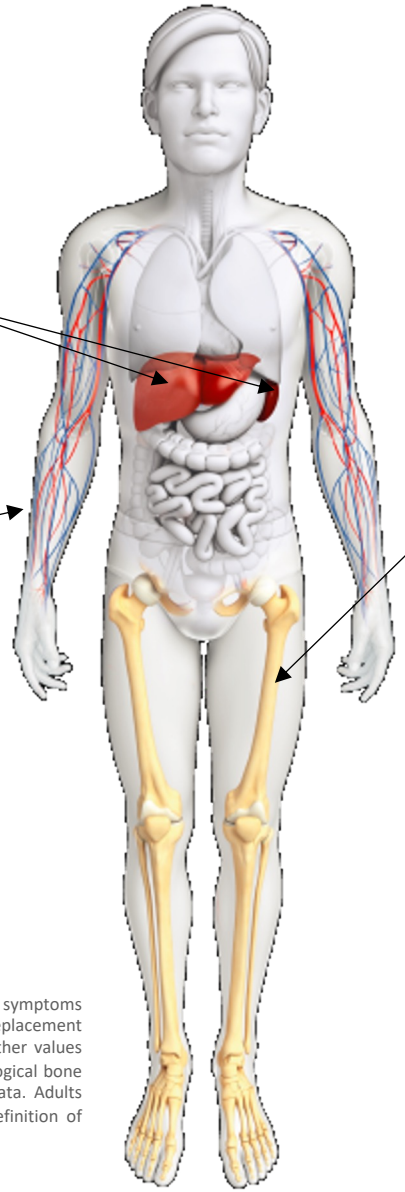
- Avascular osteonecrosis
- Osteoporosis
- Pathological fractures
- Chronic bone pain

1. Grabowski GA, Petsko GA, Kolodny EH. Gaucher Disease. In: Valle D, Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A, Gibson K, Mitchell G. eds. New York, NY: McGraw-Hill; 2014. http://ommbid.mhmedical.com/content.aspx?bookid=971&Sectionid=62643884. Accessed August 03, 2015.

Clinical presentation in adults

Hepatomegaly (79%)
Splenomegaly (87%)

Anemia (64%)
Thrombocytopenia (57%)
MGUS, multiple myeloma



General symptoms:

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

Bone involvement

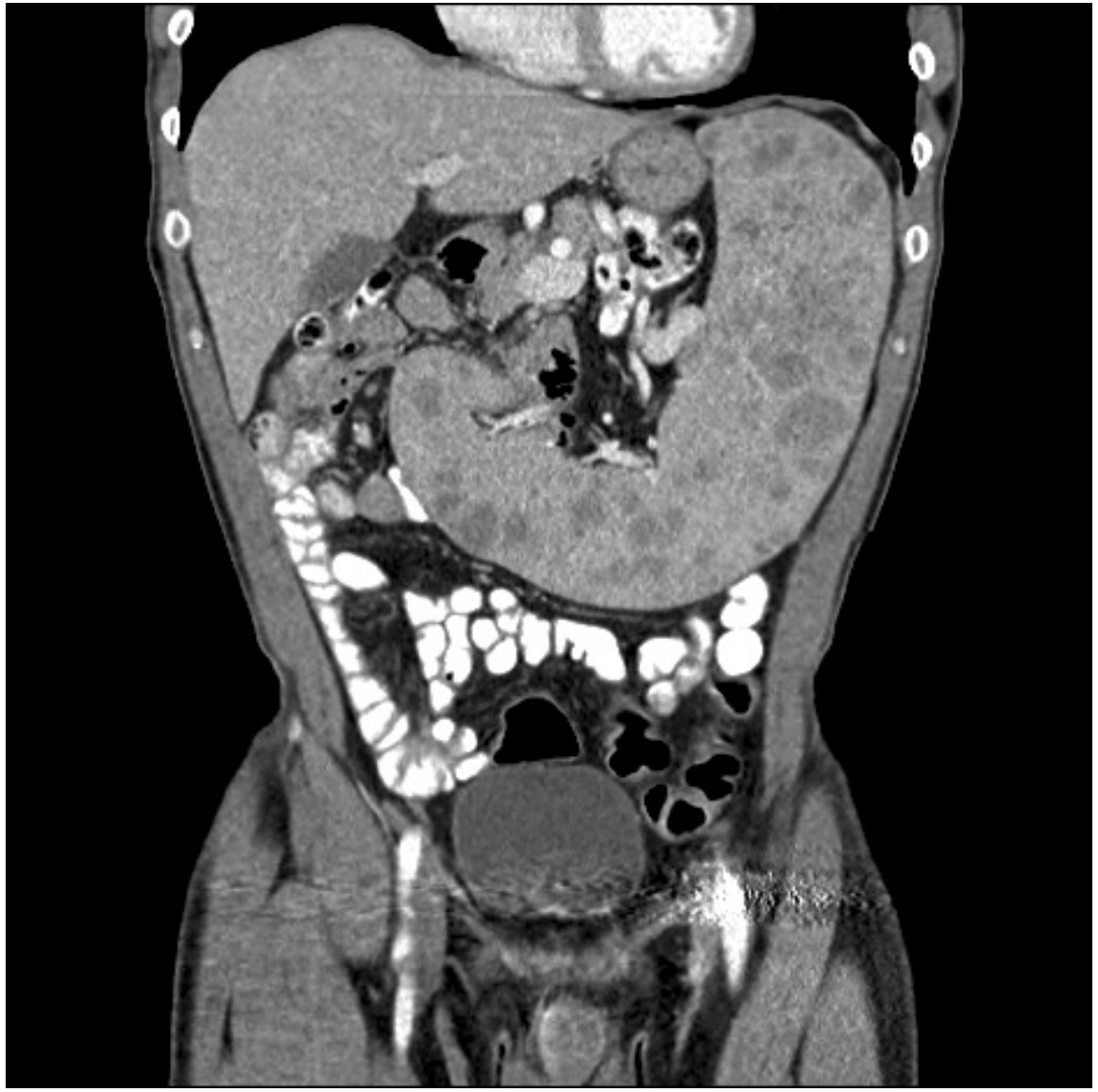
- **Bone pain - 63%**
- **Bone crisis - 33%**
- **Radiologic evidence of bone disease - 94%**
  - Erlenmeyer flask deformity - 46%
  - Bone marrow infiltration - 40%
  - Osteopenia - 42%
  - Avascular necrosis - 25%
  - Infarction - 25%
  - Lytic lesions - 8%
  - Fracture - 15%
  - Joint collapse - 8%

* Percentages of visceral and hematological symptoms show patients presenting symptoms at the latest measurement before first infusion for patients receiving enzyme replacement therapy (ERT), and last available measurement for patients not receiving ERT. Other values represent the percentages of patients with a history of bone symptoms or radiological bone disease. Outcomes presented in this study were acquired from ICGG registry data. Adults data: 1698 patient (94% type 1). Refer to the scientific publications for the definition of clinical manifestations.

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

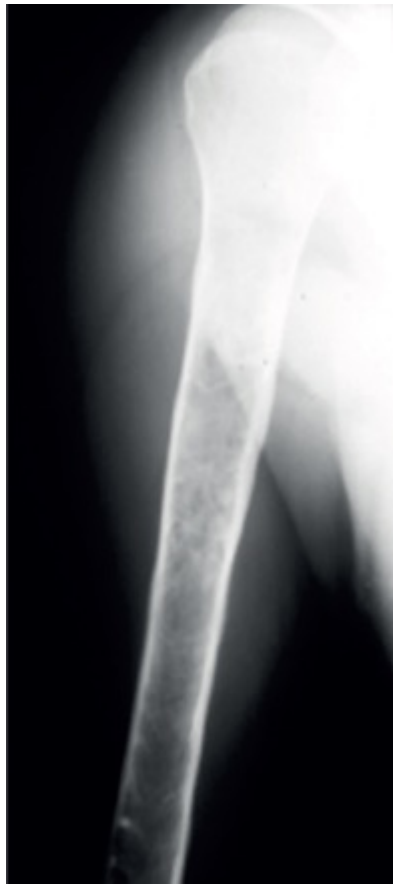
Splenomegaly

Don’t you dare splenectomise!!
- worse bone disease
- worse liver disease
- lung infiltration
…



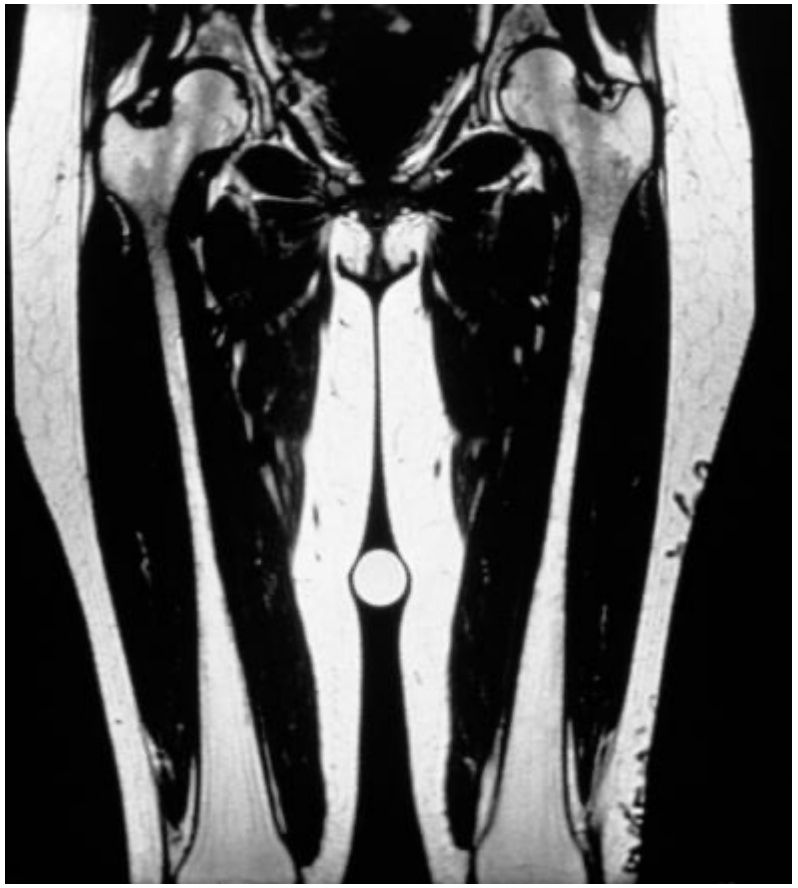
Gaucher disease - Bone manifestation

Osteopenia



Images courtesy of Prof L.W. Poll

Marrow infiltration by MRI



Images courtesy G. Grabowski

And avascular necrosis!

1. Giuffrida G, et al. Adv Ther 2014; 31:1197-1212
2. Pastores GM, Patel MJ, Firooznia H. Bone and joint complications related to Gaucher's disease. *Curr Rheumatol Rep* 2000;2:175-180.

Diagnostic testing

1

GBA-1 ENZYME ACTIVITY ANALYSIS

DBS

2

ENZYME ACTIVITY CONFIRMATION ON LEUCOCYTES

DBS

ou

Whole blood sample

3

***GBA* Genotyping**

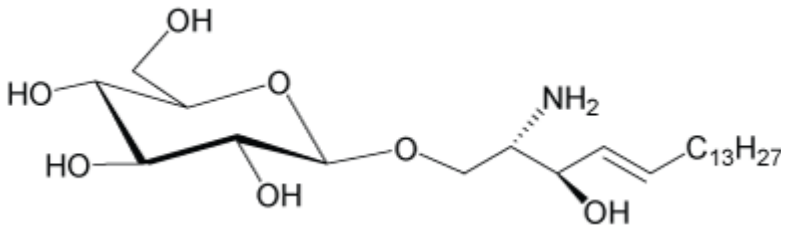
Whole blood sample

Nowadays: dual testing for GD ànd ASMD!!!!!!!

Biomarkers for Gaucher disease

- ✓ Chitotriosidase, component of the innate immune system, shows markedly elevated activity in most Gaucher disease patients. Not Gaucher specific, and not applicable in all patients. Marker of macrophage activity

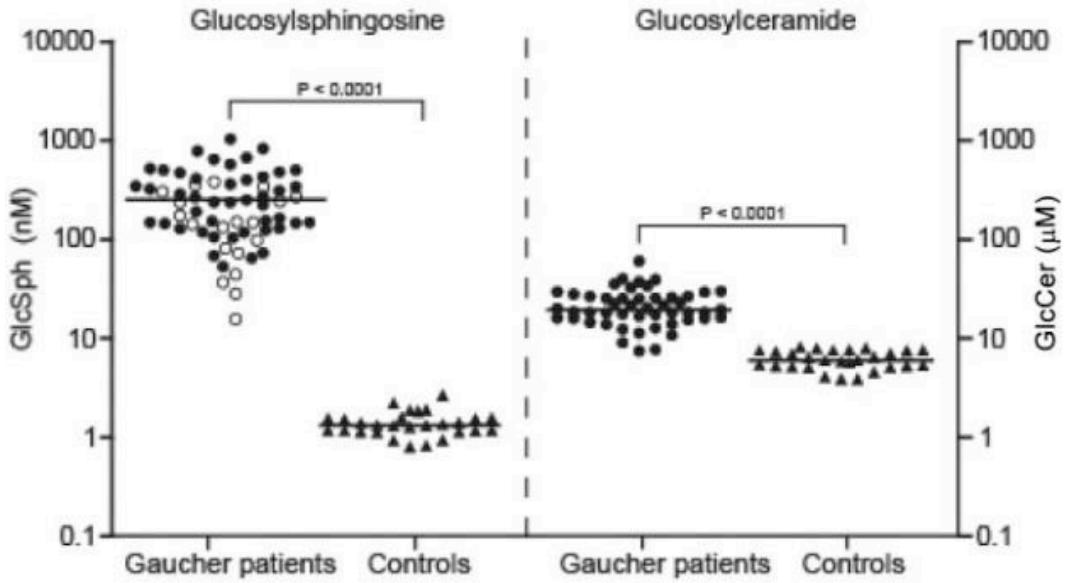
- ✓ Accumulating lyso-GL-1 (glucosylsphingosine)

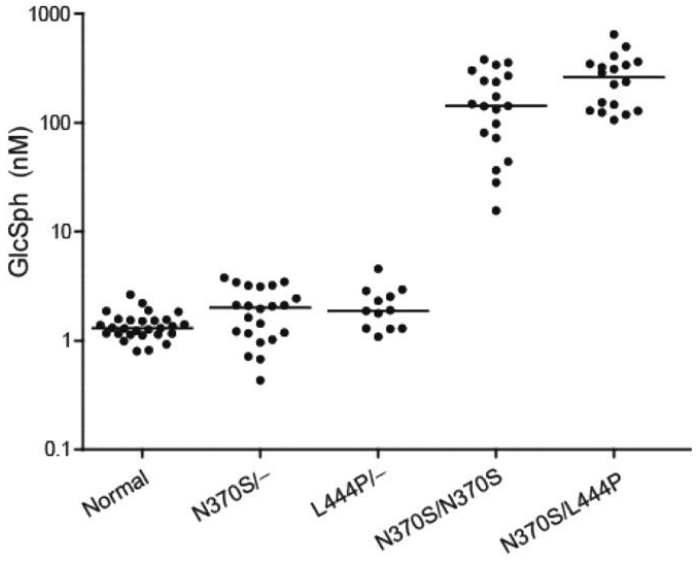


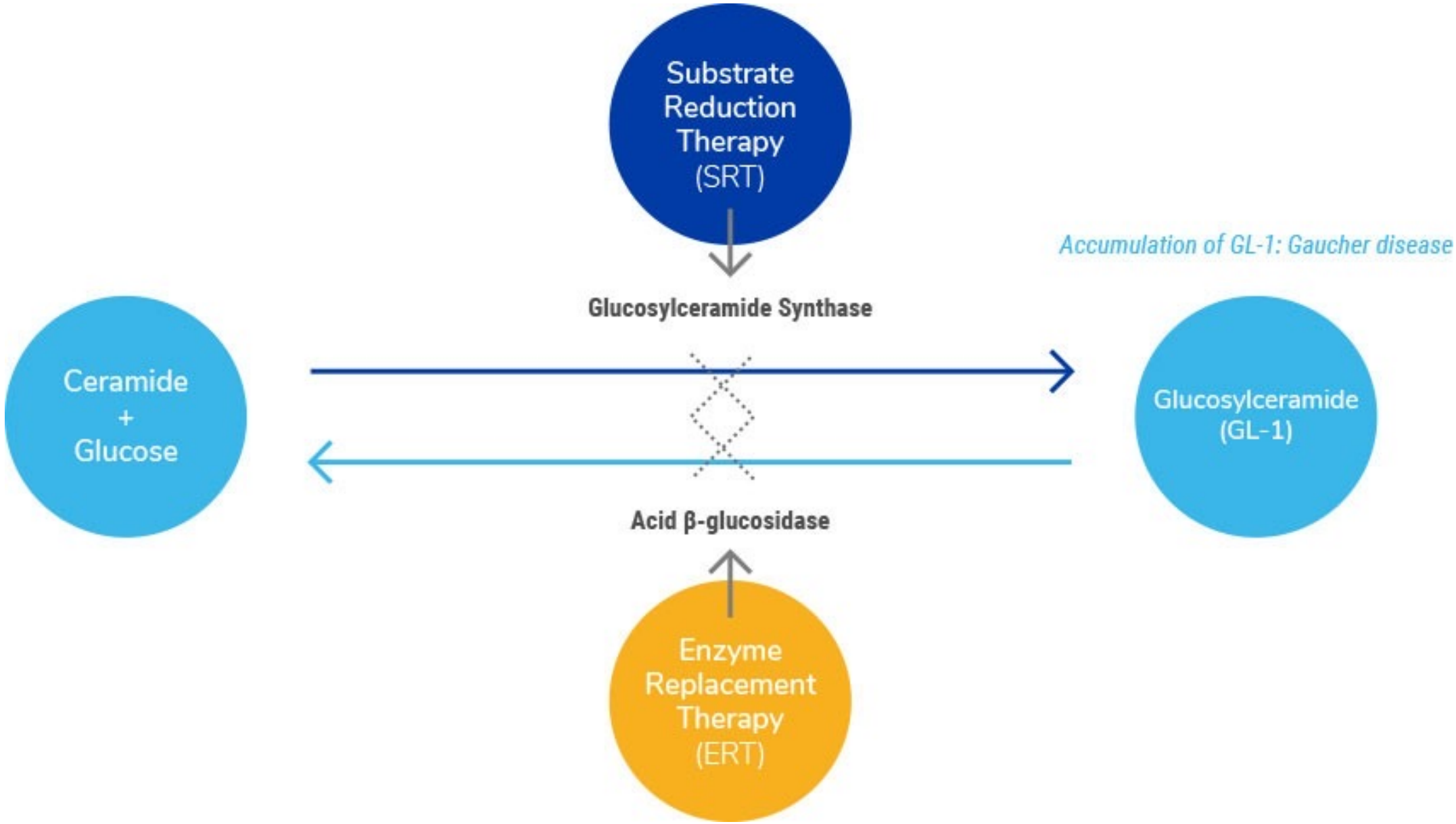
lyso-GL-1

Lyso-GL-1

- High specificity.
- Levels are in accordance with disease severity






Substrate Reduction Therapy (SRT)
Accumulation of GL-1: Gaucher disease
Glucosylceramide Synthase
Ceramide + Glucose
Glucosylceramide (GL-1)
Acid β-glucosidase
Enzyme Replacement Therapy (ERT)

Treatment for Gaucher disease

- Enzyme replacement therapy: /15d IV (Cerezyme, Vpriv, Elylyso)
- Substrate reduction therapy: miglustat, eliglustat, venglustat

- Bisphosphonates, Ca/D3, prosthesis of the hip/shoulder/knee…
- Portal hypertension: varices surveillance, carvedilol/propranolol
- Cirrhosis: HCC surveillance (US/6m)
- MGUS: you know