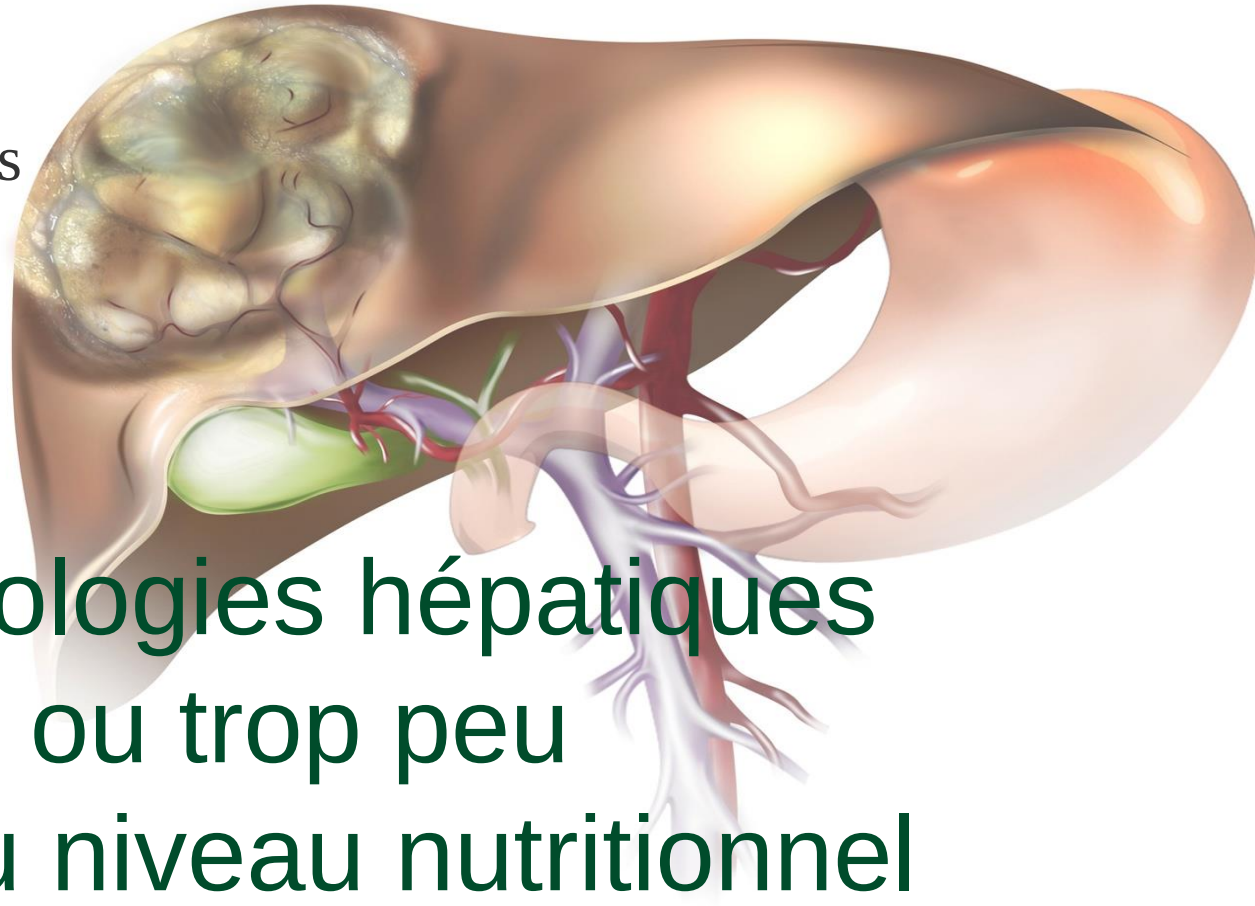
SwissMilk
Symposium pour diététicien/nes
Hotel Continental, Lausanne
19 Septembre 2023
09:10-09:55



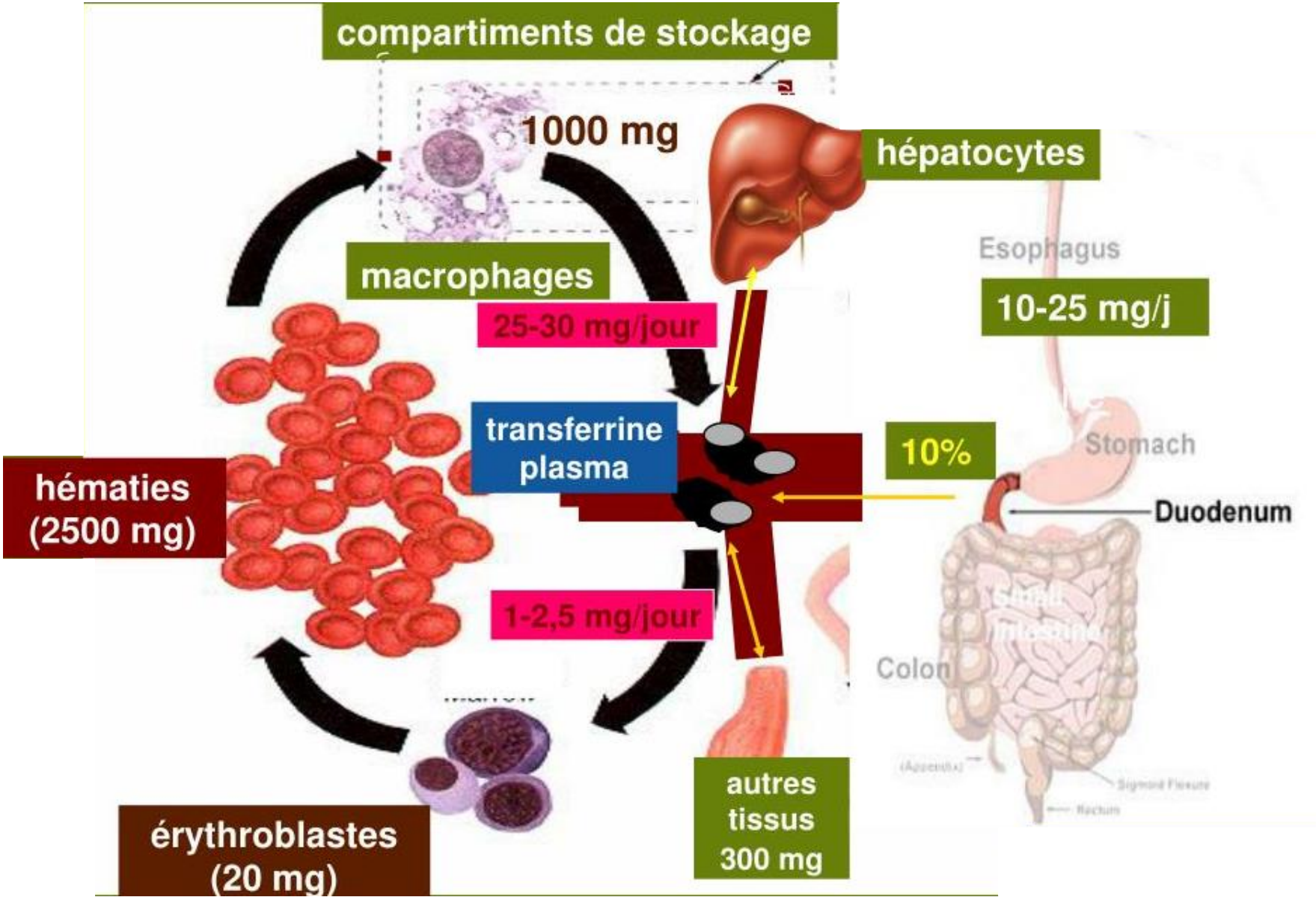
Fer et pathologies hépatiques
Trop ou trop peu
Que faire au niveau nutritionnel

Prof. Jean-François Dufour
jf.dufour@svmed.ch

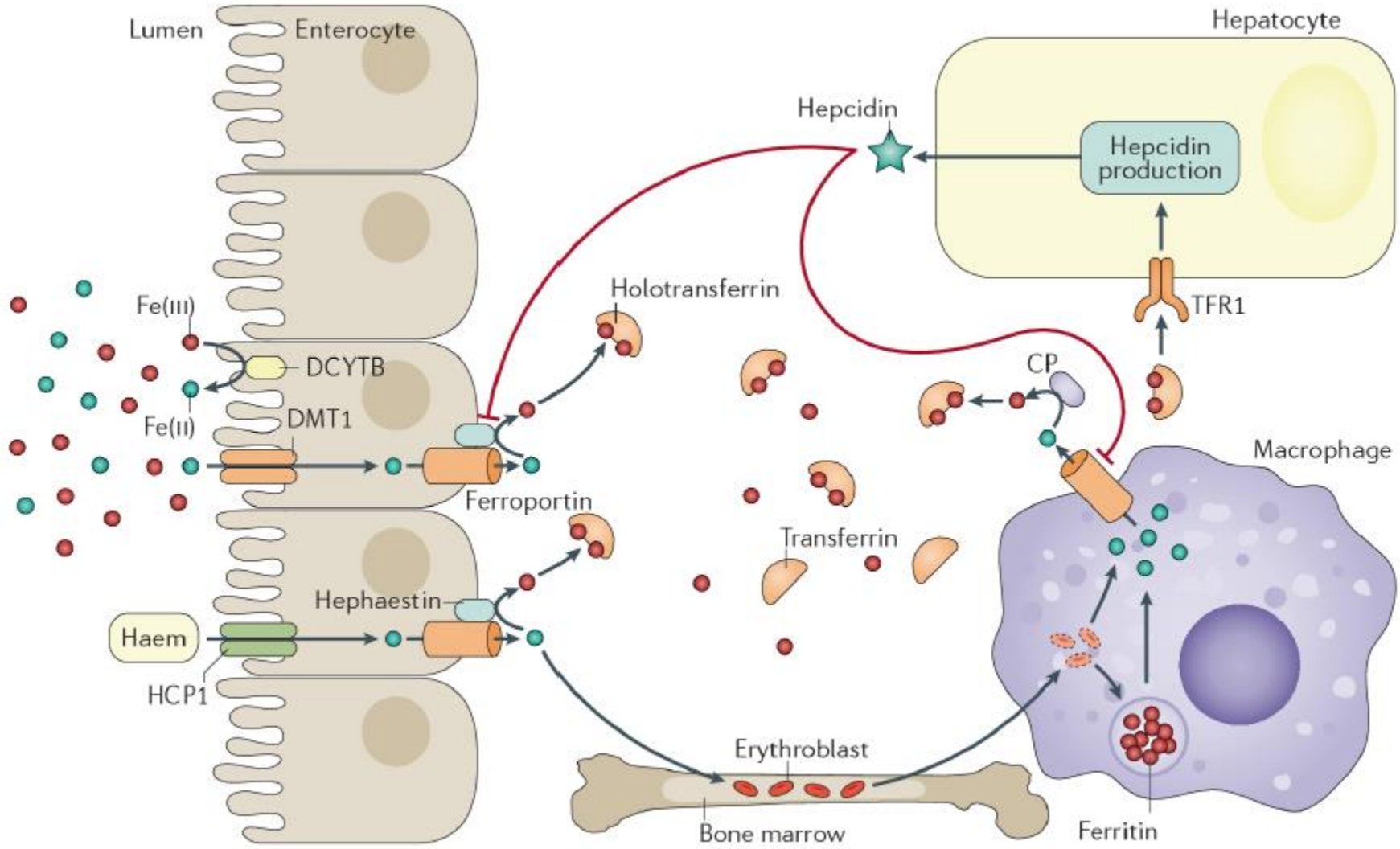
Selon Suétone, plusieurs signes annoncent la mort de César dans les jours précédant les ides de mars, mais il n'en tient pas compte. L'haruspice Spurinna, lors d'un sacrifice, lui demande de se méfier des Ides.

Un haruspice, ou aruspice, est un pratiquant de l'haruspicine, l'art divinatoire de lire dans les entrailles d'un animal sacrifié (notamment l'hépatoscopie : examen du foie censé représenter l'univers)

Le fer dans l'organisme



Le fer dans l‘organisme



Brissot et al. Nat Rev Dis Primers 2018

Paramètres du fer

Fer sérique

Transferrine
Saturation de la transferrine

Ferritine

Facteurs affectant absorption

Decrease:

- **Decreased gastric acidity**
- Phytates in grains
- Tannates in tea
- Phosphates
- Some vegetable proteins
- Cow's milk proteins

Increase:

- Ascorbic acid
- Human breast milk

Polyphenolic compounds widely found in coffee and tea such as chlorogenic acids, monomeric flavonoids, and polyphenol polymerization products strongly inhibit dietary nonheme-iron absorption.

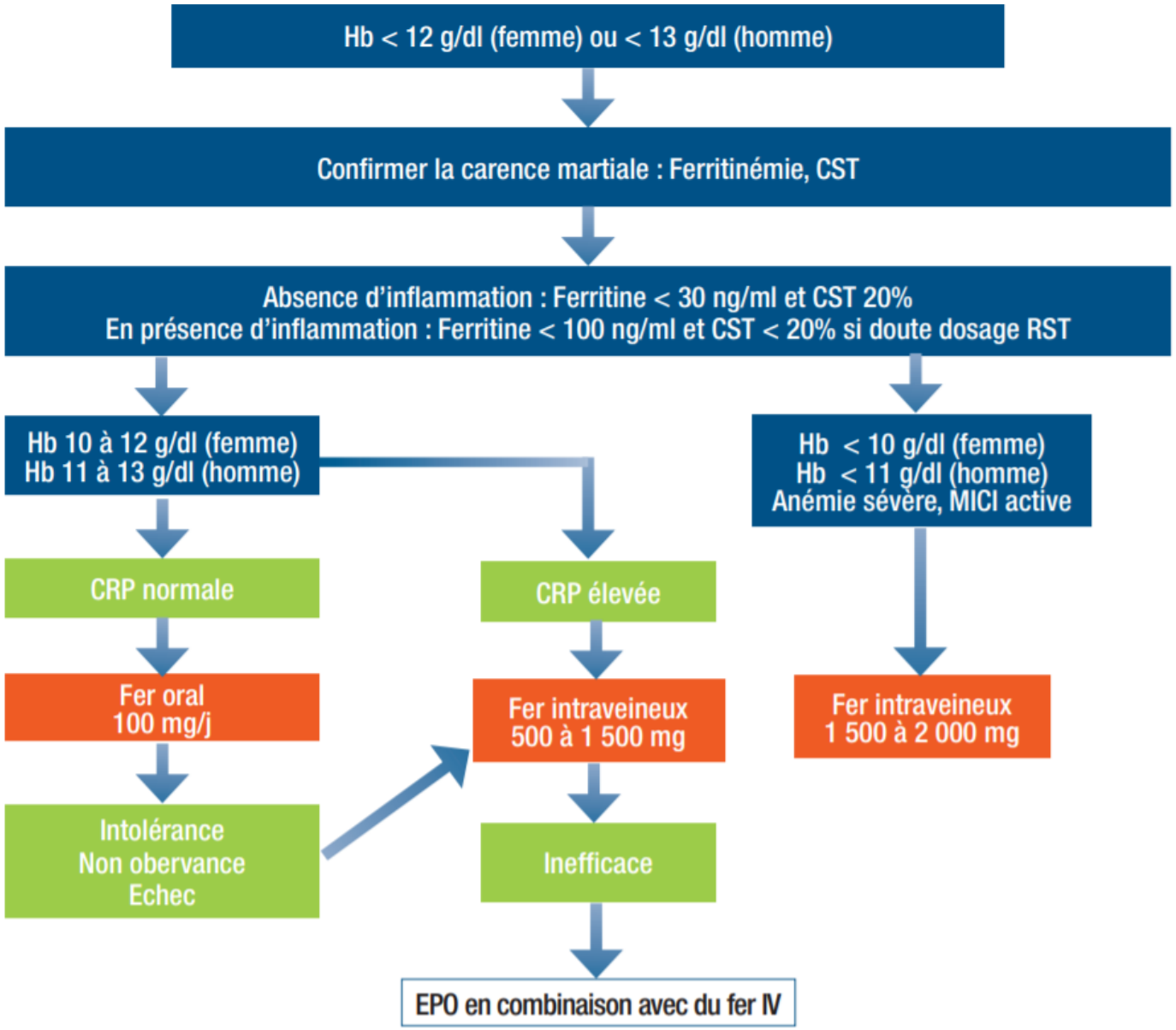
Piskin et al. ACS Omega 2022

Carence martiale

Occult GI blood loss	
Common	
Aspirin/NSAID use	10–15%
Colonic carcinoma	5–10%
Gastric carcinoma	5%
Benign gastric ulceration	5%
Angiodysplasia	5%
Uncommon	
Oesophagitis	2–4%
Malabsorption	
Common	
Coeliac disease	4–6%
Gastrectomy	<5%
Helicobacter pylori colonisation	<5%
Non-GI blood loss	
Common	
Menstruation	20–30%

Hardy et al. Int J Rhumatol 2015

Seuils vers trop peu: carence martiale



Préparations avec du fer

- *Monothérapie*
- Ferinject
- FerMed
- Ferro Gradumet
- ferro sanol
- Ferrum Hausmann
- Maltofer
- MonoFer
- Tardyferon
- Venofer

- *Combinaison*
- Addaven
- Andreavit
- Duofer
- Eisen Biomed
- Elevit
- Fero-Folic-500
- gyno-Tardyferon
- Kendural
- Maltofer
- Nutryelt
- Pharmaton

- *Combinaison*
- Premavid
- Supradyn
- Supradyn
- Tracutil
- Vitarnin

Fer(III)-oxidhydroxid-Saccharose

Velphoro

(HyperP dans IRC)

Hypophosphatémie après fer iv

Randomised, double-blind, clinical trial at 20 outpatient hospital clinics in Europe (Austria, Denmark, Germany, Sweden, UK). Adults with IBD and iron deficiency anaemia (IDA) were randomised 1:1 to receive ferric carboxymaltose (FCM) or FDI (ferric derisomaltose).

Incident hypophosphataemia occurred in 8.3% (4/48) FDI-treated patients and in 51.0% (25/49) FCM-treated patients (adjusted risk difference: -42.8% (95% CI -57.1% to -24.6%) $p<0.0001$).

Zoller et al. GUT 2023

Recommandations pour iv administration

Setting	Guideline	Rationale[a]
Heart failure with reduced ejection fraction	ESC 2021[12]	IV iron, if ferritin <100 µg/L or ferritin <300 µg/L and TSAT <20%
Chronic kidney disease, stage ≥III	NICE 2021[14]	Anemia and ID based on ferritin ≤800 µg/L and HRC, CHr or TSAT; IV iron only in patients requiring dialysis or erythropoiesis stimulating agents
Pregnancy (2nd/3rd trimester)	SGGG 2017[21]	IV iron in the presence of anemia requiring rapid correction, or severe anemia (Hb < 90 g/L)
Postpartum	SGGG 2017[21]	IV iron for medium to severe anemia (Hb < 95 g/L); oral iron in case of mild anemia (Hb < 120 g/L)
Cancer (chemotherapy)	ESMO 2018[22]	IV iron in the presence of anemia and ID based on ferritin <100 µg/L or ferritin 100–800 µg/L[23] and TSAT <20%
Inflammatory bowel disease	ECCO 2015[13]	IV iron in the presence of anemia, active inflammation, and ferritin ≤100 µg/L
Preoperative	Muñoz 2016/17[24]	IV iron, if surgery in <6 weeks, Hb < 130 g/L and ID based on ferritin <30 µg/L or ferritin 30–100 µg/L and TSAT <20% or CRP > 5 mg/L
Postoperative (major surgery)	Muñoz 2018[25]	IV iron, if ID based on ferritin <100 µg/L or ferritin <300 µg/L and TSAT <20% or CHr < 28 pg; IV iron, if Hb < 100 g/L and preoperative anemia or heavy surgical bleeding

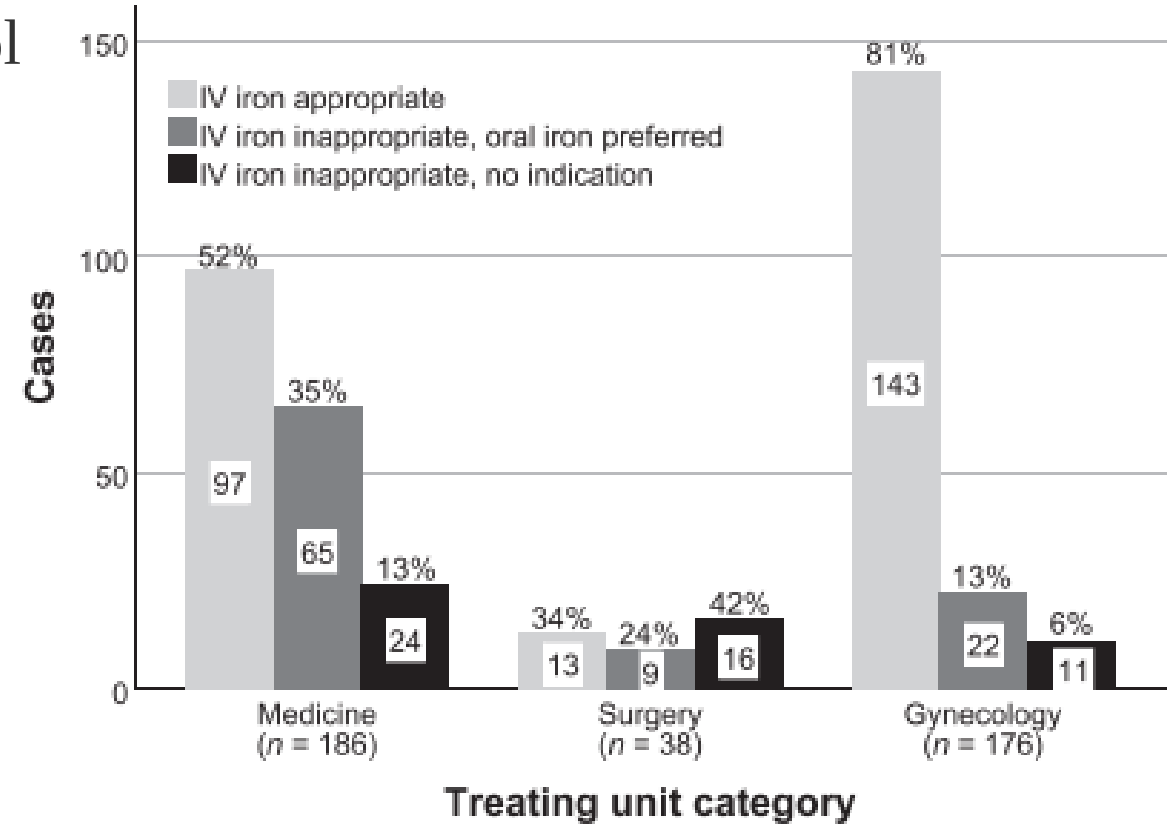
Abbreviations: CHr, reticulocyte hemoglobin; CRP, C-reactive protein; Hb, hemoglobin; HRC, hypochromic red blood cells; ID, iron deficiency; IV,

Ritter et al. Europ J hematol 2023

Recommandations pour iv administration

Swiss retrospective quality control study at a tertiary care hospital, more than one third (37%) of IV iron infusions in the inpatient sector were inappropriate according to current guidelines.

Appropriate prescribing gynecological patients 81%, Medicine patients 52% surgical departments 34%.



Ritter et al. Europ J hematol 2023

Seuils vers trop

- **Hyperferritinaemia**

  > 300 µg/L (men) / > 200 µg/L (women)

- **Transferrinsaturation (TS, %)**

  normal < 50% (men) / < 45% (women)

$$\frac{\text{serum iron (µmol/L) x 400}}{\text{transferrin (mg/dL)}}$$

Transferrin:

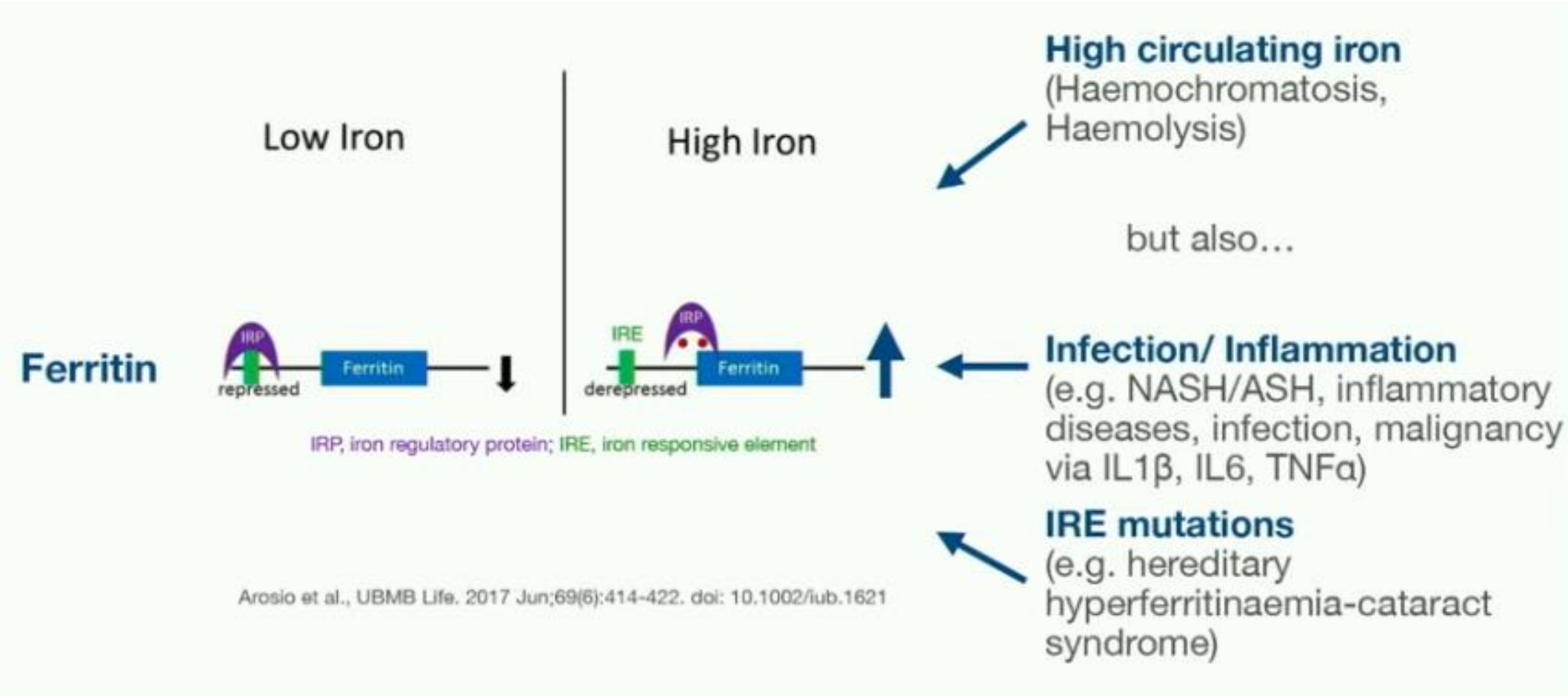
- protein, produced in liver
- carries iron in the circulation

high inter-individual variability (age, gender, ethnicity)

- fasting did **not** reduce variability!

Adams et Barton, J Hepatol 2011

Synthèse de la ferritine



Hyperferritinémie

Retrospective outpatient referrals for serum ferritine.
482 chart reviewed,
119 with ferritin > 1000 ug/L

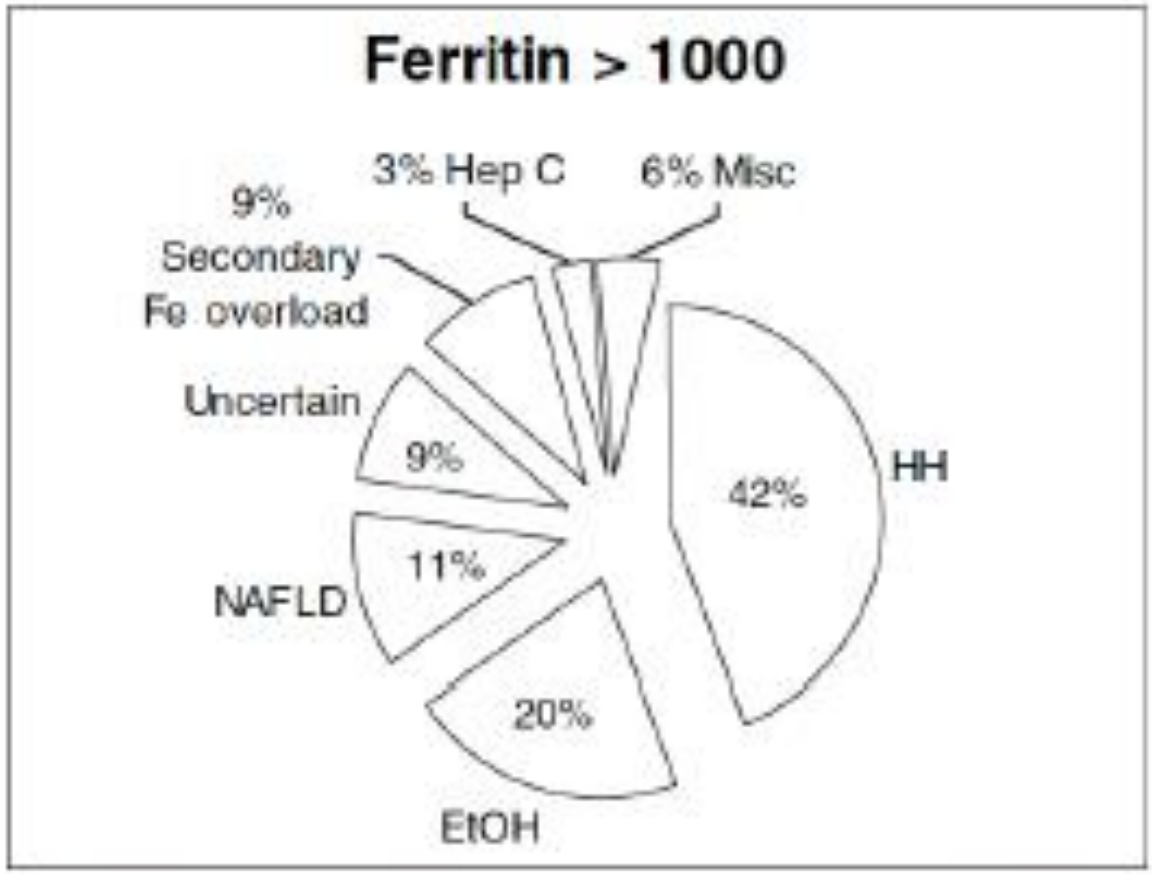
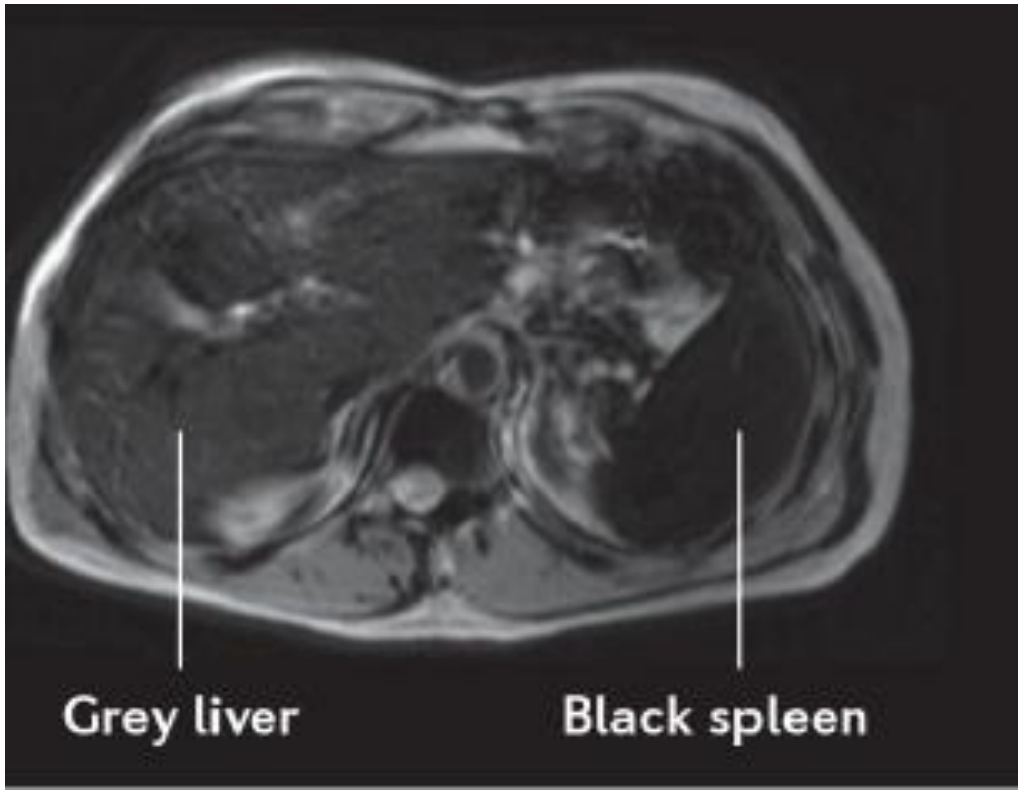
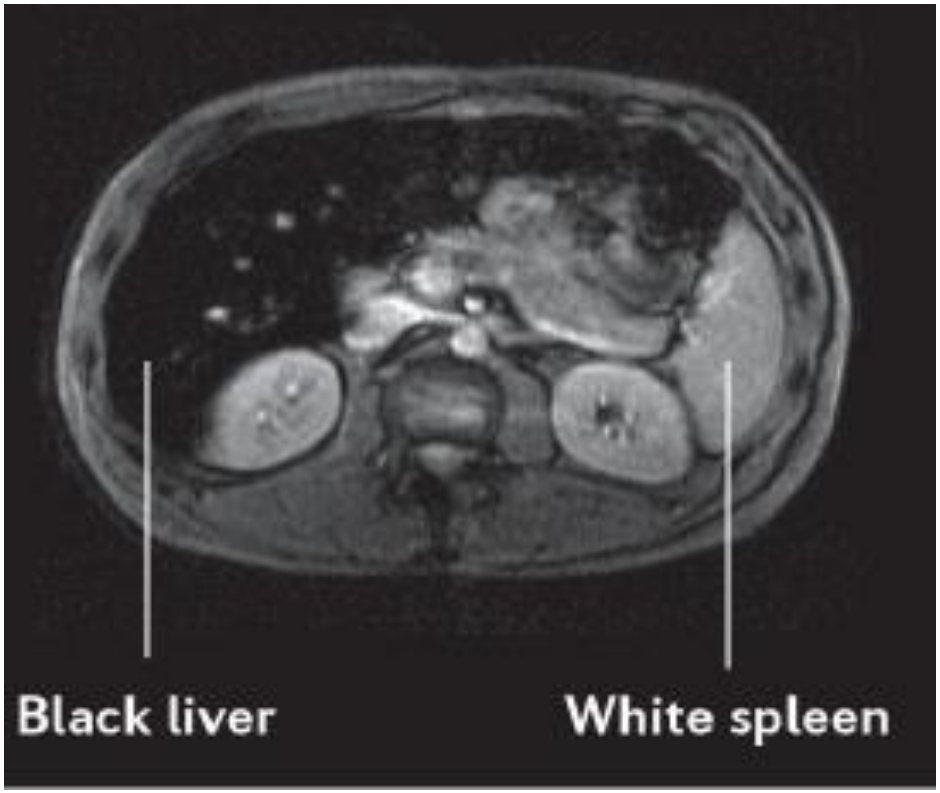


Figure 1) *Diagnoses in patients (n=119) with elevated ferritin (Fe) (greater than 1000 µg/L). EtOH Alcoholic liver disease; Hep C Hepatitis C; HH HFE-related hemochromatosis; Misc Miscellaneous; NAFLD Nonalcoholic fatty liver disease*

Wong et al. Can J Gastroenterol 2006

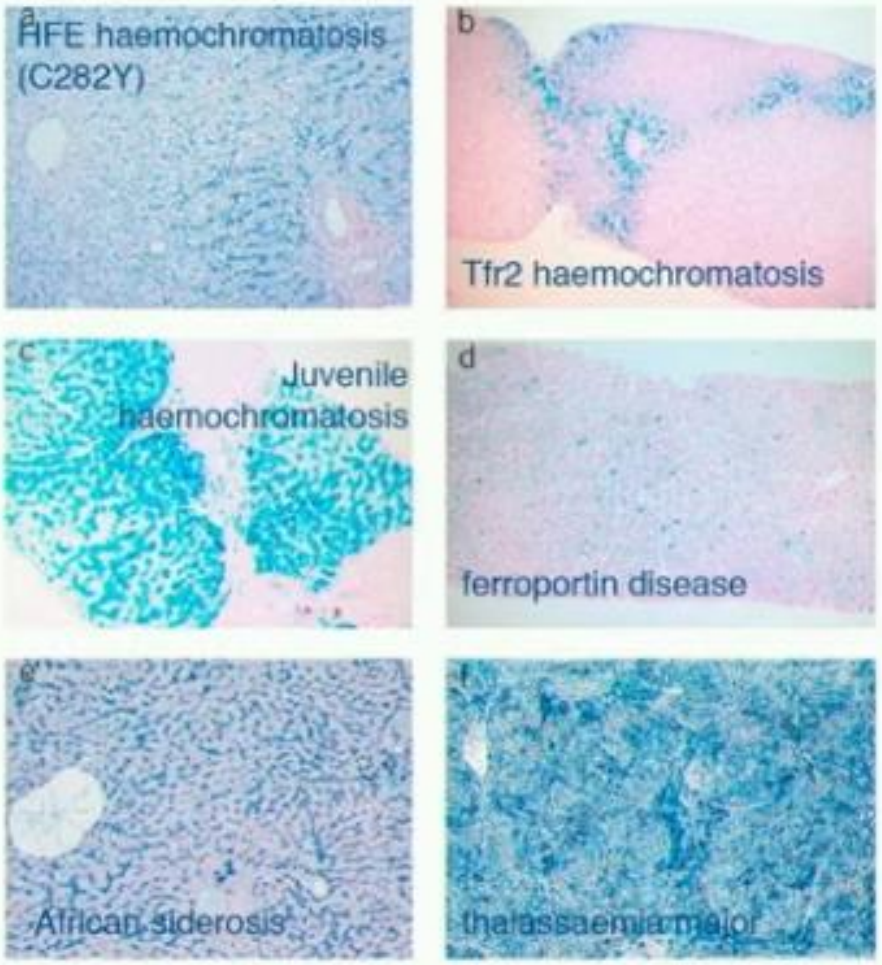
Trop de fer dans le foie





Brissot et al. Nat Rev Dis Primers 2018

Trop de fer dans le foie



ACG Clin Practise Guideline, Am J Gastroenterol 2019

1. parenchymal iron overload
   (porto-central gradient, periportal, panlobular)
   vs.
   Kupffer cell iron overload
2. hepatic iron content
   (by spectroscopy)
   > 71 µmol/g dry weight
3. staging fibrosis
4. look for concomitant liver disease

History of hereditary hemochromatosis:

- 1865, Trousseau: clinical syndrome of skin pigmentation, diabetes and cirrhosis
- 1889, von Recklinghausen: pigment in liver is iron and named the disease hemochromatosis
- 1953, Sheldon: inborn error of iron metabolism
- 1977, Simon: close linkage to HLA-A3, recessive
- 1996, Feder (Mercator Genetics): positional cloning of HFE

Discovery of hepcidin

FEBS 24035

FEBS Letters 480 (2000) 147–150

LEAP-1, a novel highly disulfide-bonded human peptide, exhibits antimicrobial activity[1]

Alexander Krause, Susanne Neitz[2], Hans-Jürgen Mägert, Axel Schulz, Wolf-Georg Forssmann, Peter Schulz-Knappe[2], Knut Adermann*

THE JOURNAL OF BIOLOGICAL CHEMISTRY

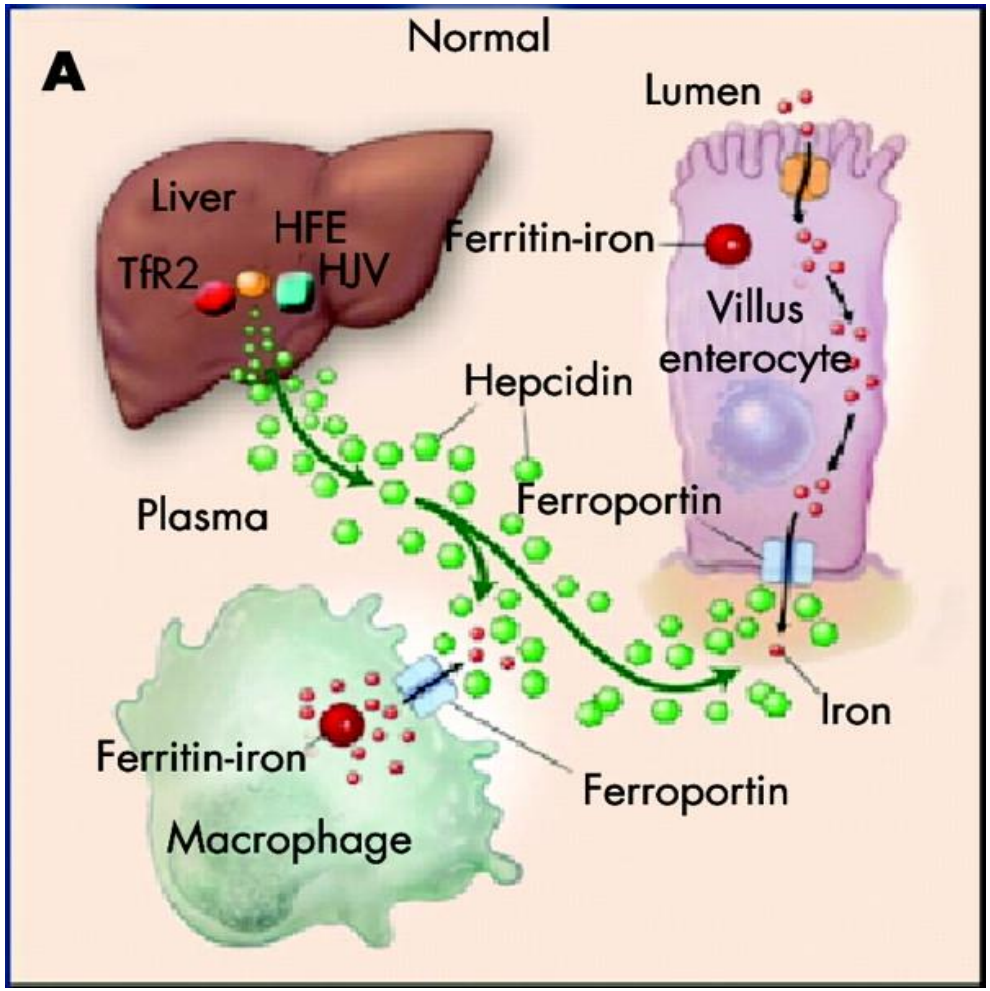
Vol. 276, No. 11, Issue of March 16, pp. 7806–7810, 2001
Printed in U.S.A.

Hepcidin, a Urinary Antimicrobial Peptide Synthesized in the Liver*

Received for publication, September 29, 2000, and in revised form, November 9, 2000
Published, JBC Papers in Press, December 11, 2000, DOI 10.1074/jbc.M008922200

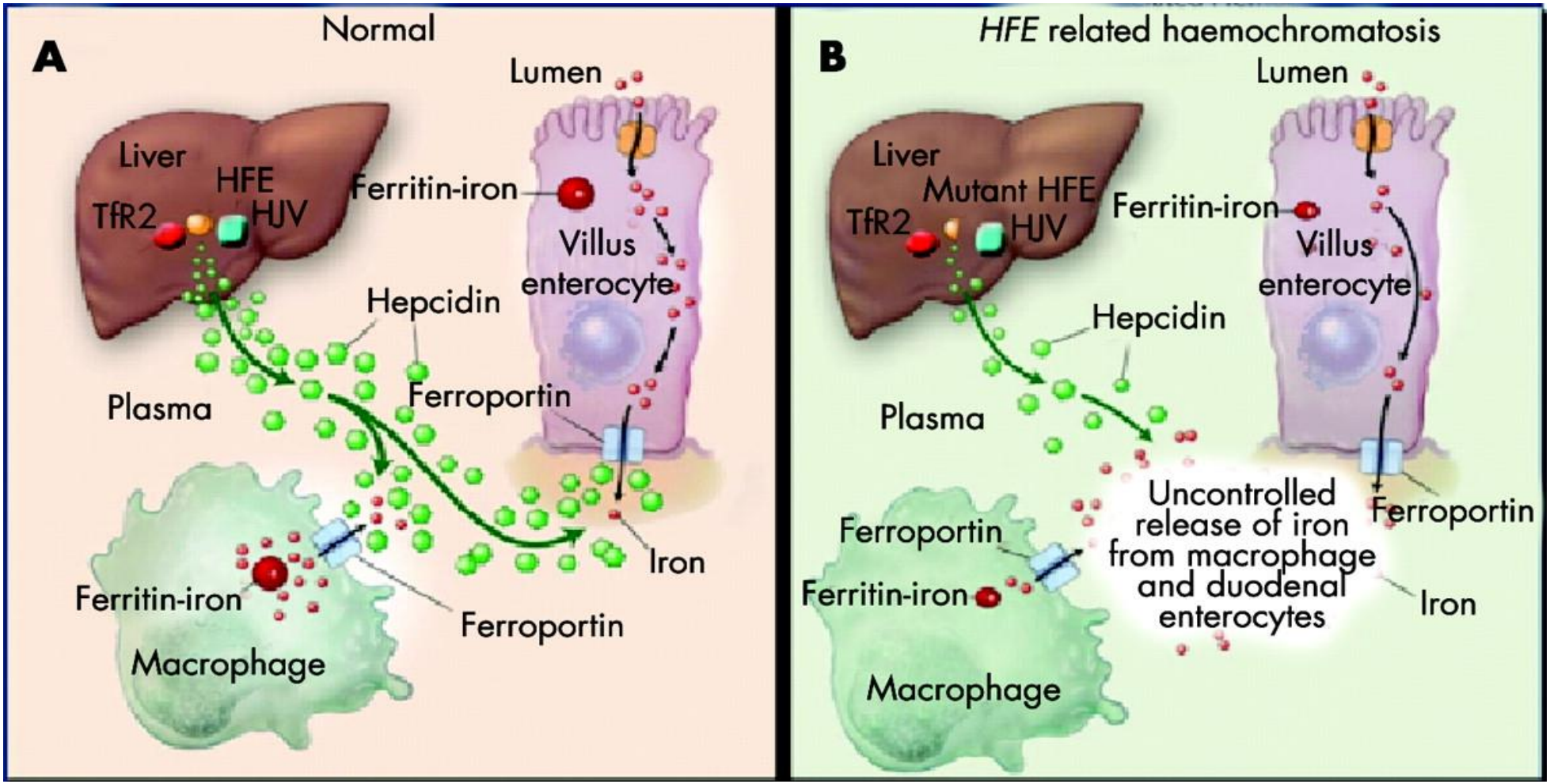
Christina H. Park‡, Erika V. Valore‡, Alan J. Waring§, and Tomas Ganz‡¶

Hepcidin Function



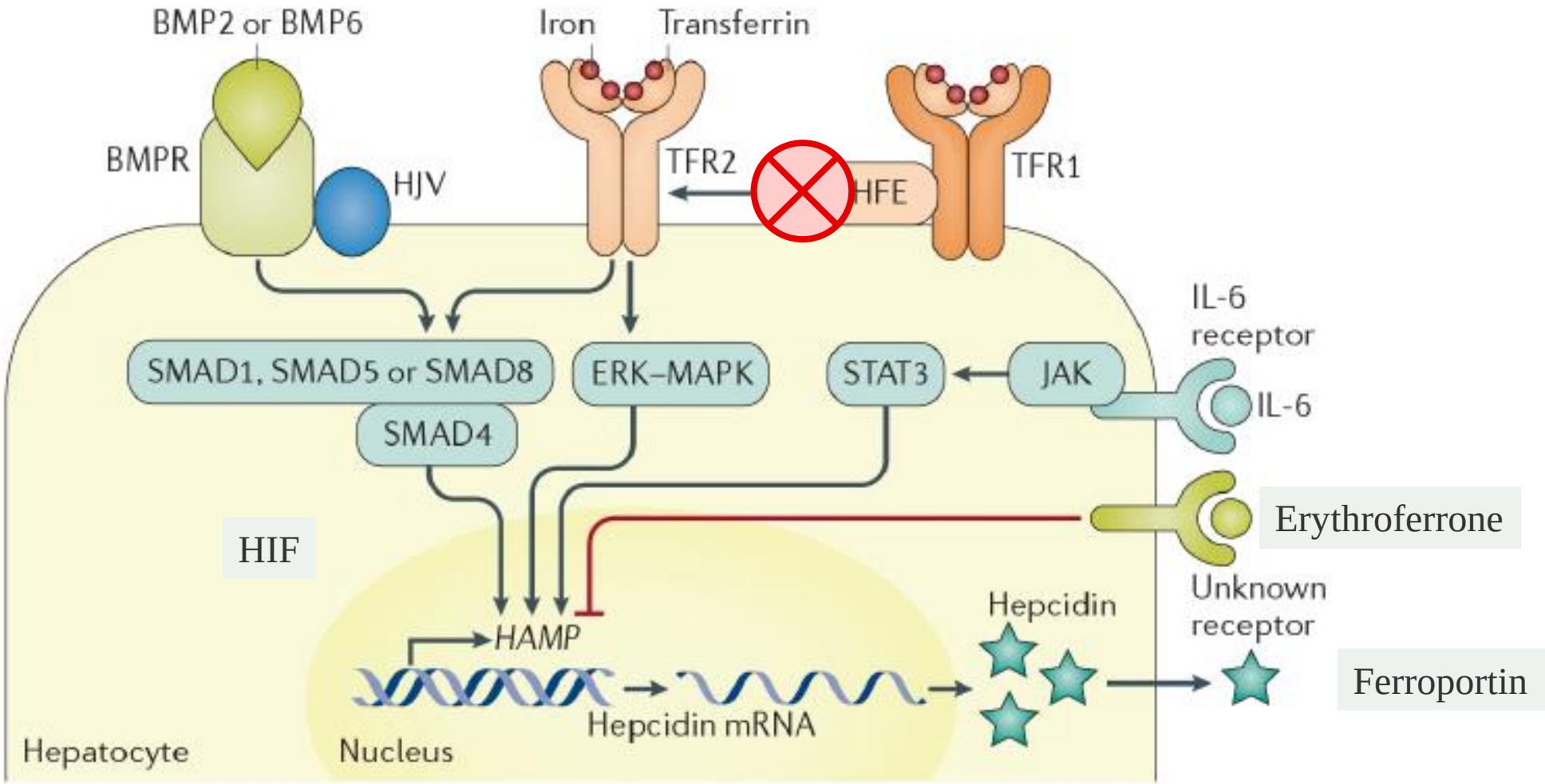
Pietrangelo. Gut 2006

Hepcidin Function



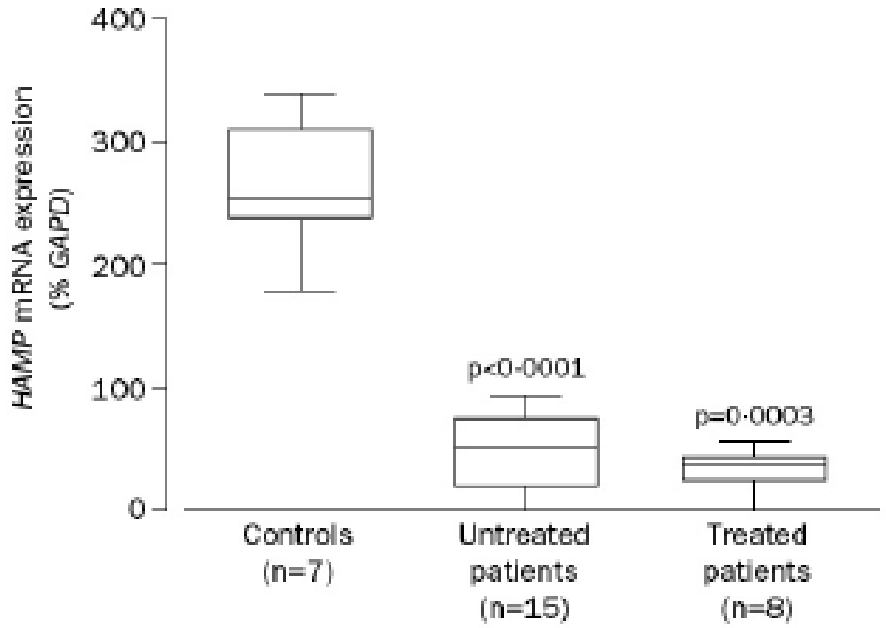
Pietrangelo. Gut 2006

Type 1 hereditary hemochromatosis



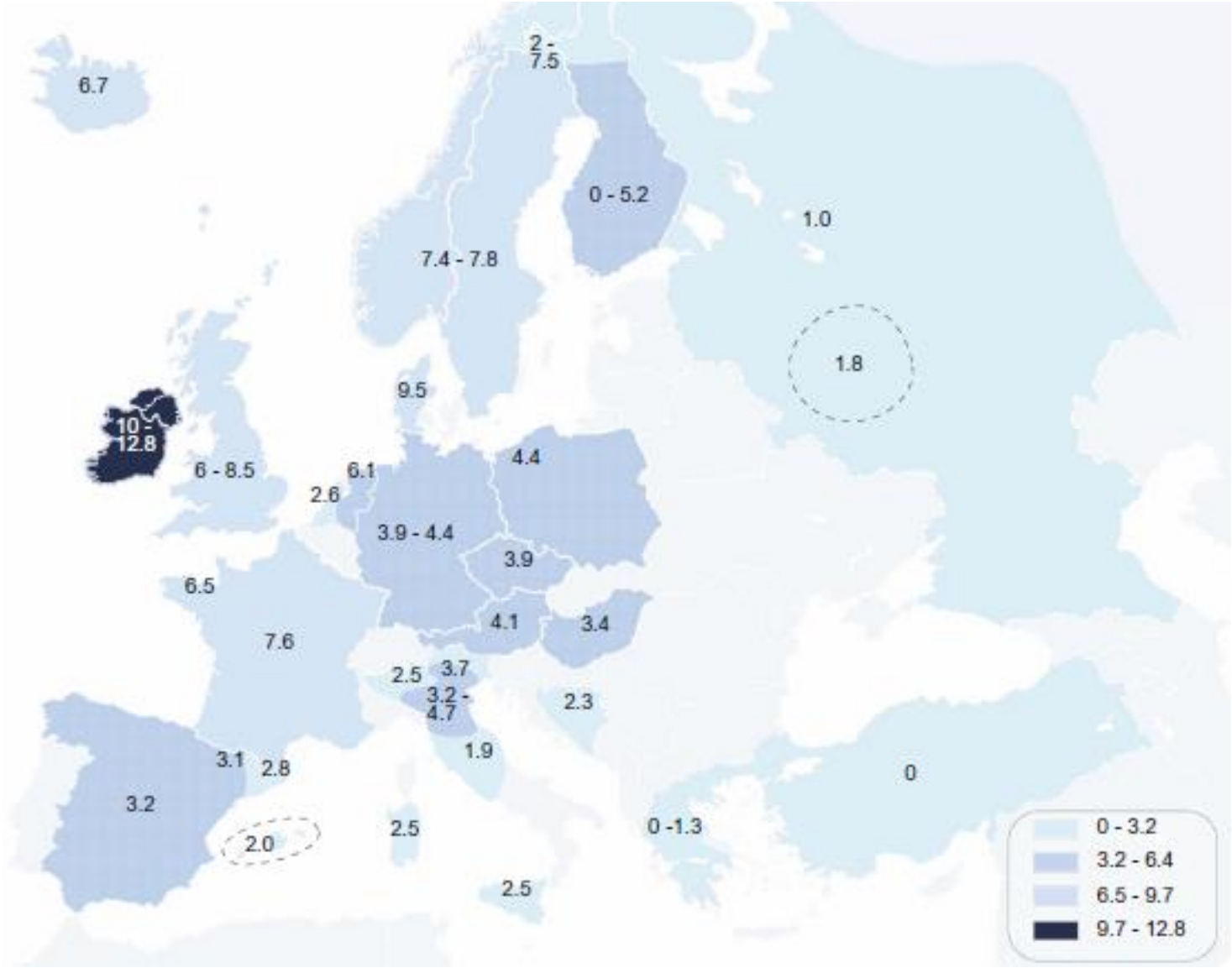
Brissot et al Nat Rev Dis Primers 2018

Low Hepcidin in HFE-Hemochromatosis



Bride et al. Lancet 2003

Frequency of C282Y allele



EASL Guidelines 2010

Variable penetrance

Only 25-60% of homozygous individuals for C282Y mutation in *HFE* gene develop a clinical hemochromatosis

Modifiers

- Gender
- Lifestyles
- Genes

Brissot et al Nat Rev Dis Primers 2018

Significance of HFE heterozygosity

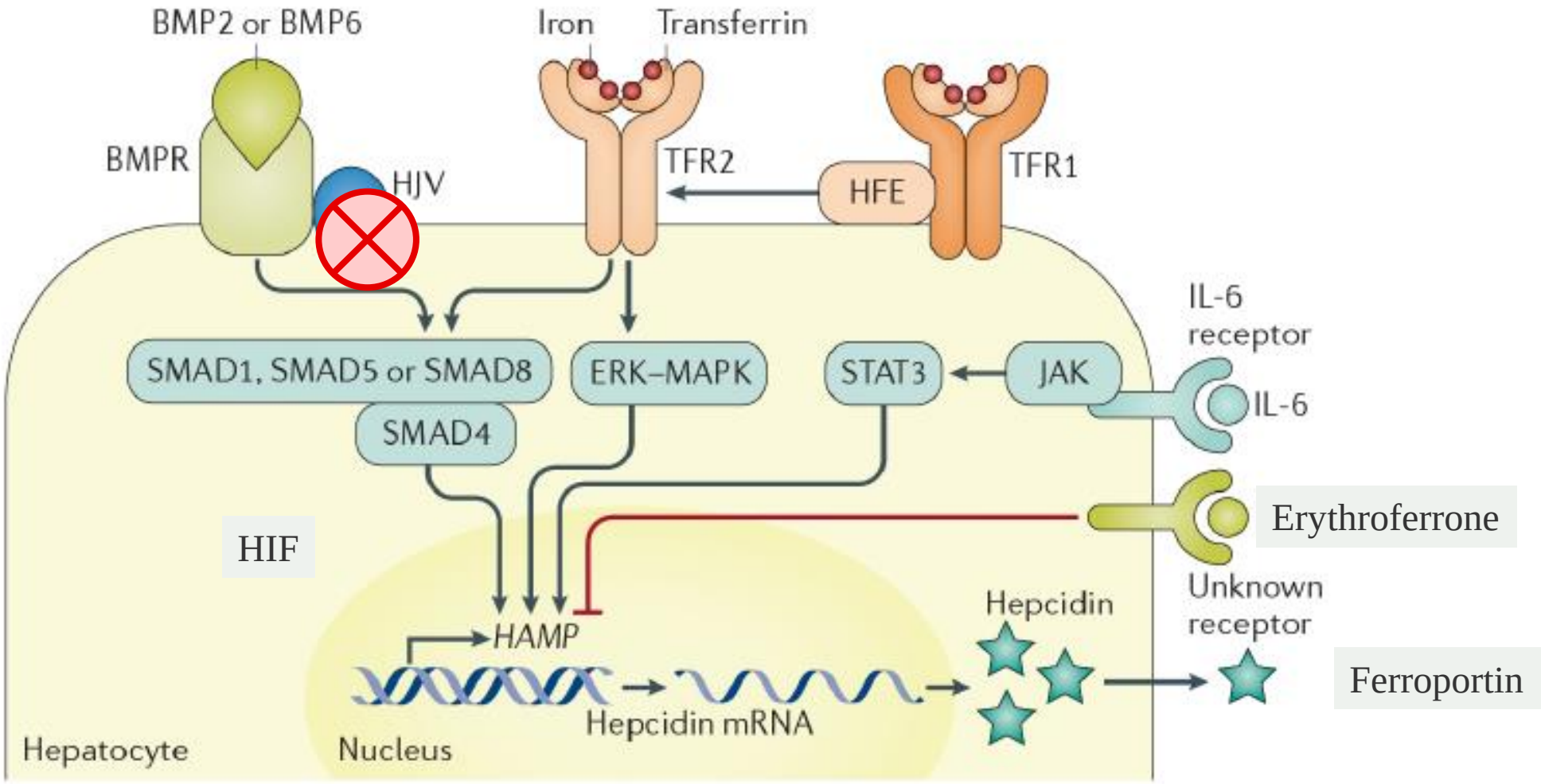
Genotyping HFE in 31,192 Northern European descents

At baseline TS>55% 3% C282Y heterozygotes, 0% H63D heterozygotes

12 years follow-up: TS levels remained similar, No heterozygotes developed iron overload

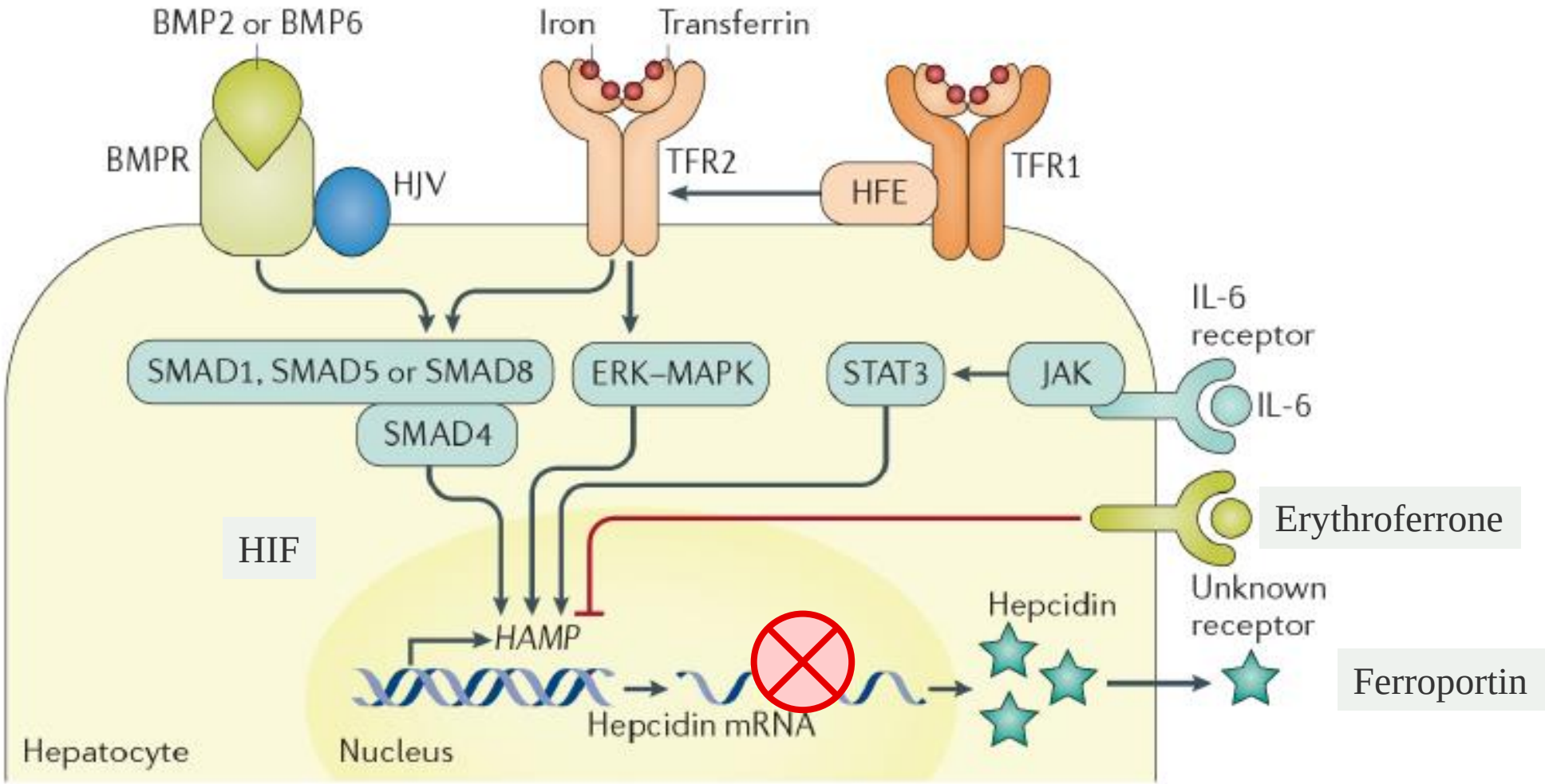
Zalounis et al J Gastro Hepatol 2014

Type 2A hereditary hemochromatosis



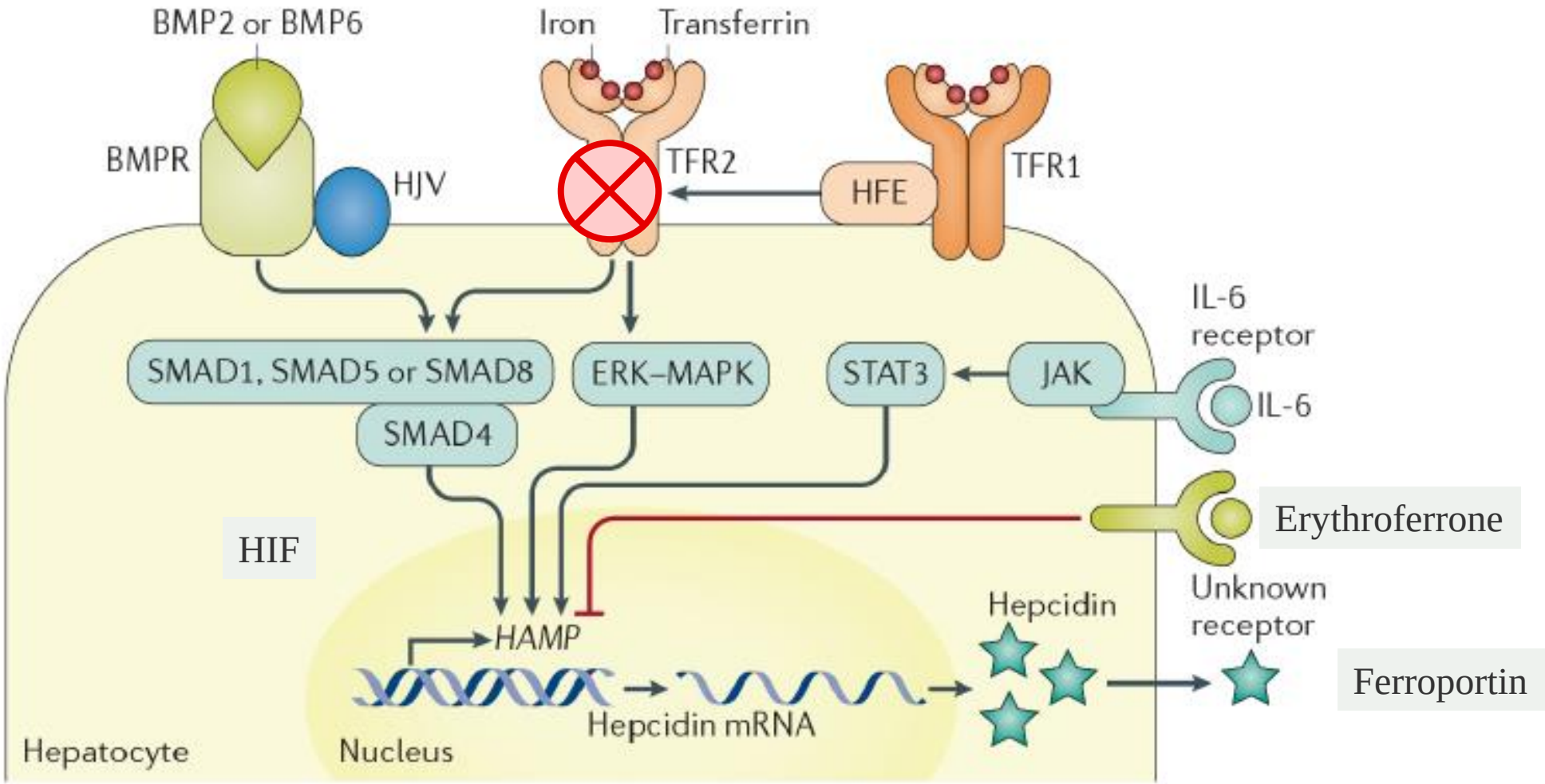
Brissot et al Nat Rev Dis Primers 2018

Type 2B hereditary hemochromatosis



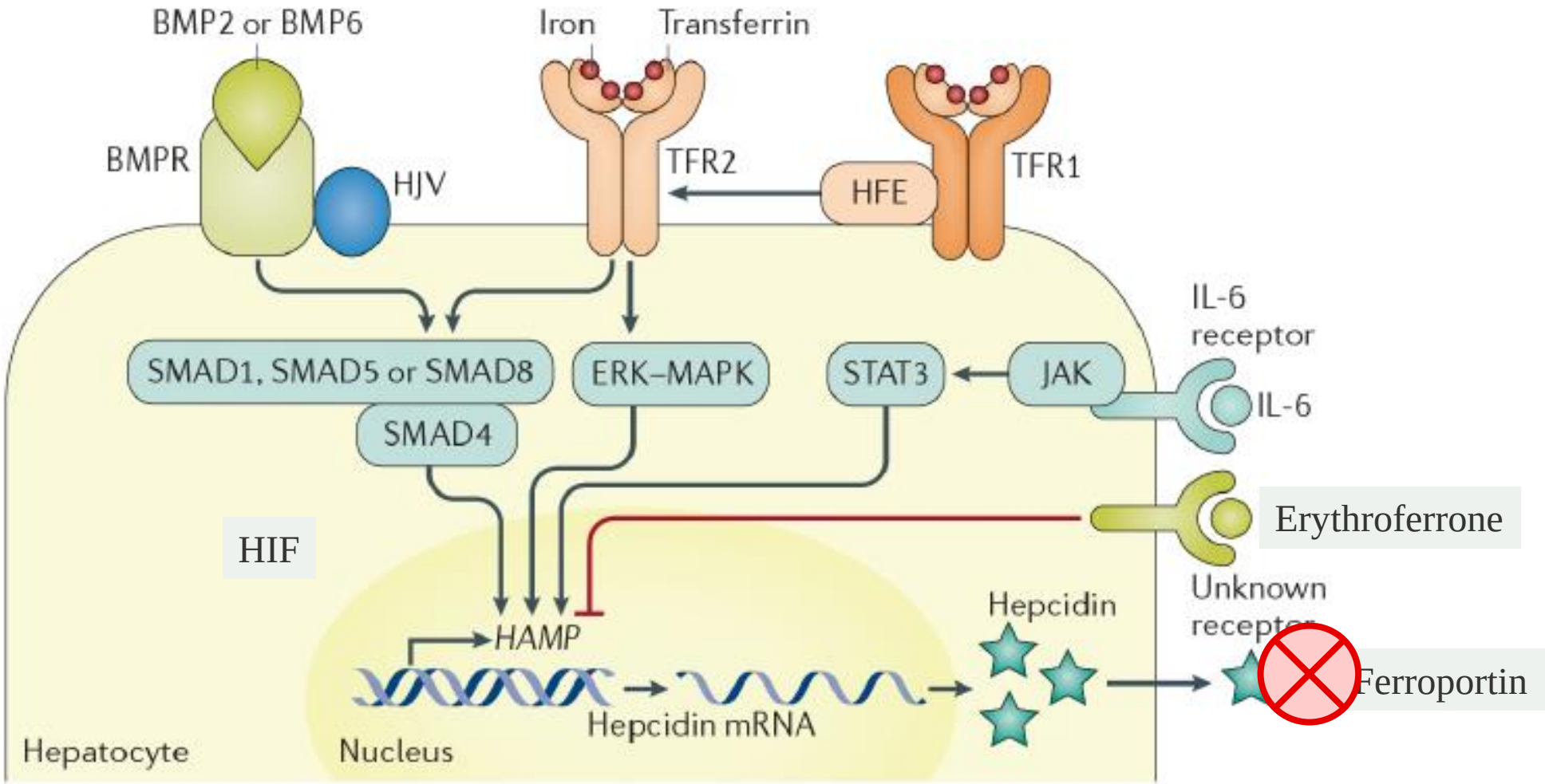
Brissot et al Nat Rev Dis Primers 2018

Type 3 hereditary hemochromatosis



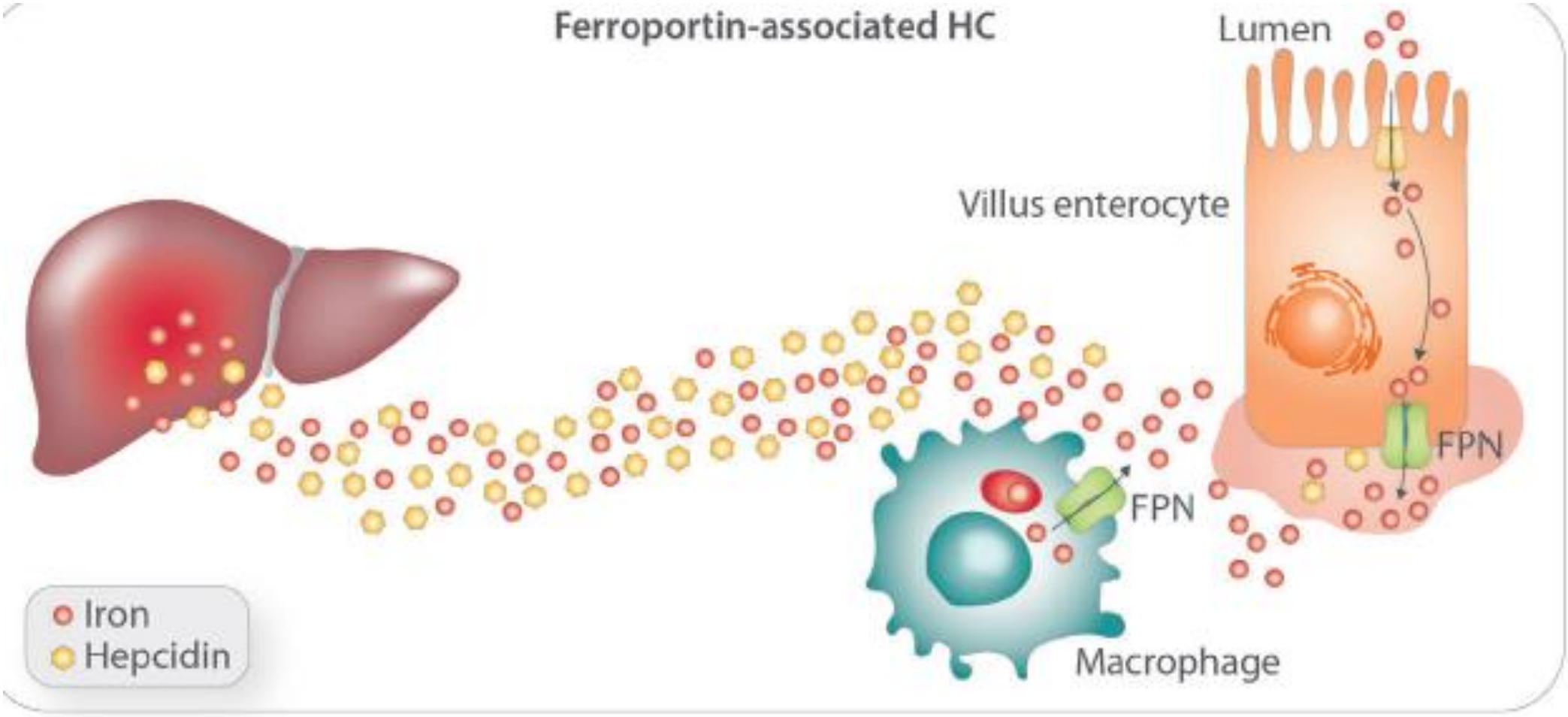
Brissot et al Nat Rev Dis Primers 2018

Type 4 hereditary hemochromatosis



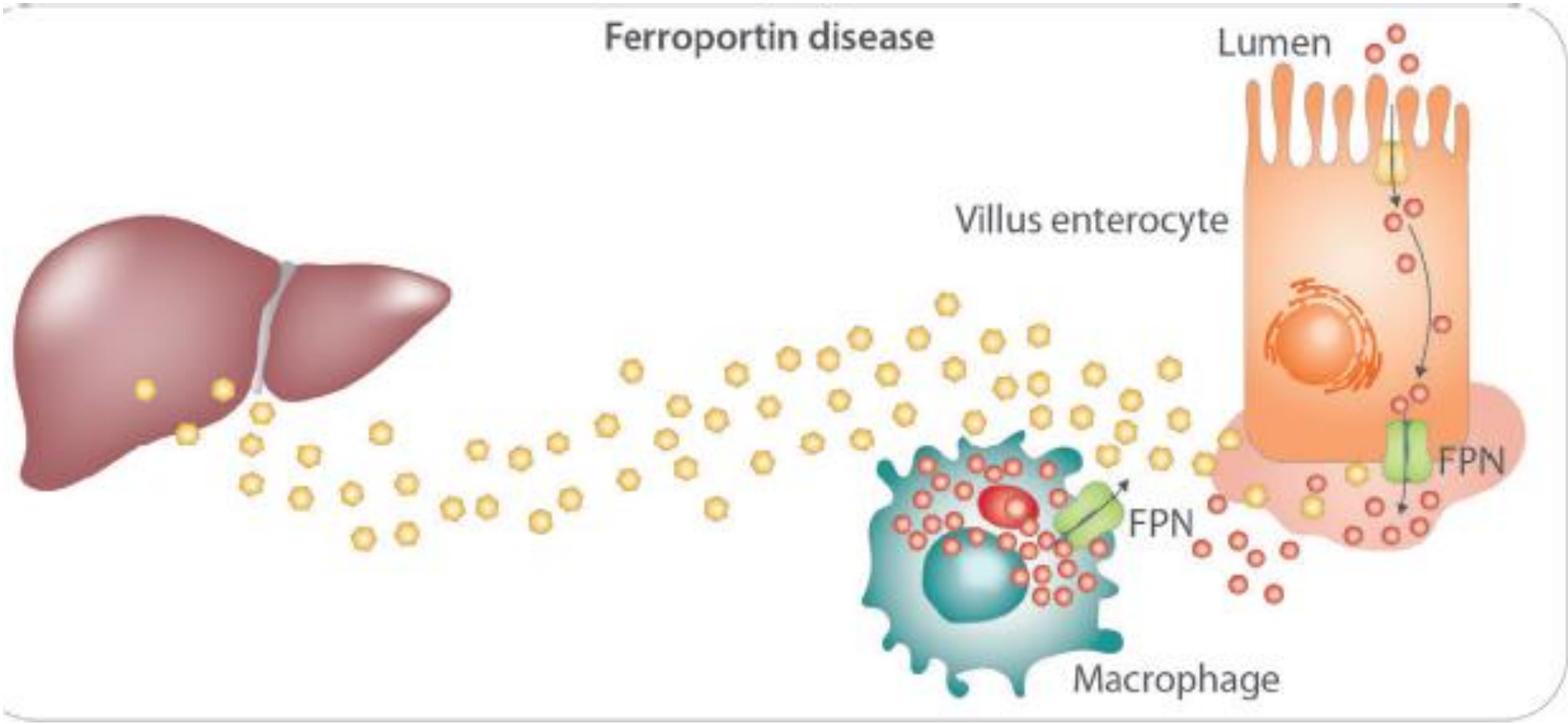
Brissot et al Nat Rev Dis Primers 2018

Ferroportin gain-of-function mutation



Pietrangelo. Hematologica 2017

Ferroportin lack-of-function mutation



Pietrangelo. Hematologica 2017

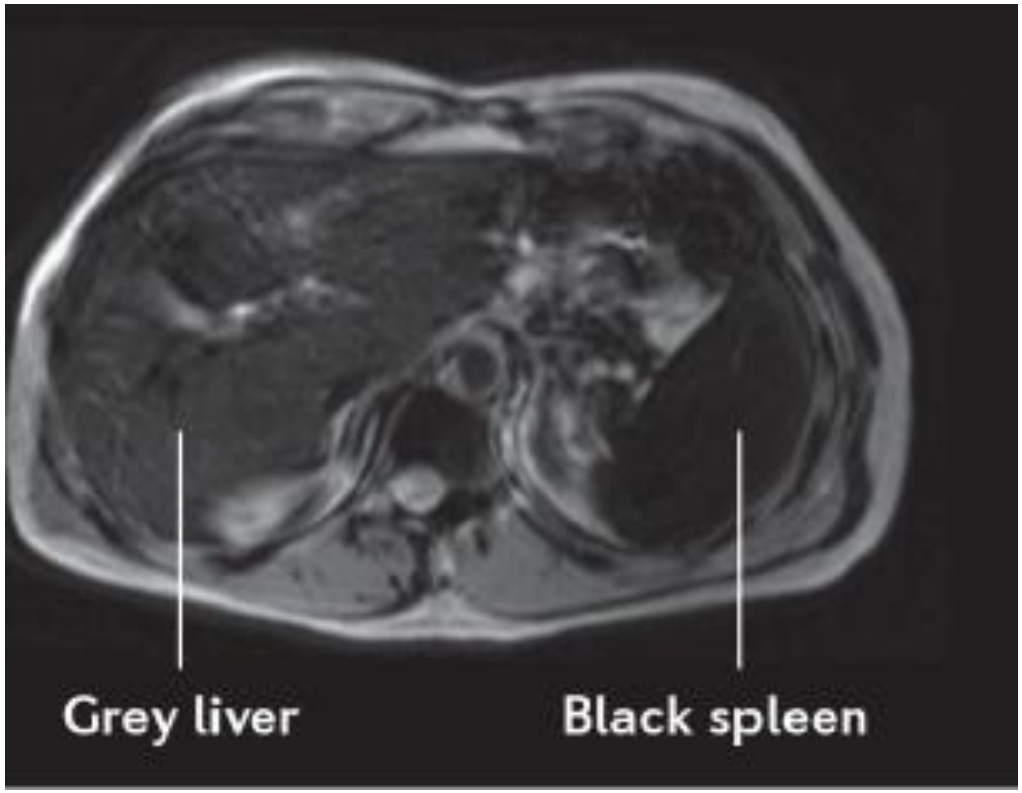
Ferroportin mutations

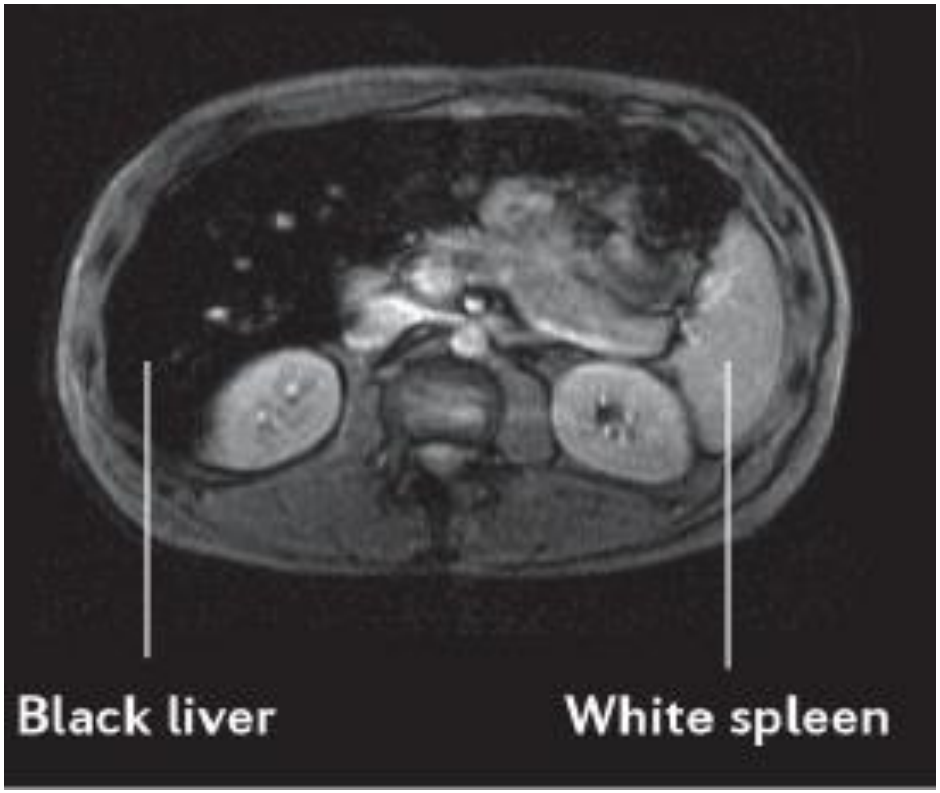
	Classical (4A)	Non-classical (Ferroportin associated HC)
Mutations	A77D, V192del, G80S	N144H, C326Y, C326S, C326F
Inheritance	Autosomal-dominant	Autosomal-dominant
Ferritin	High	High
Transferrin-Saturation	Normal-low	High
Iron Overload	Macrophages	Hepatocytes
Pathophysiology	Ferroportin lack-of-function mutations (impaired iron-export capability of ferroportin) 1. Somewhat limit iron export in enterocytes 2. Severly affect iron export from macrophages	Ferroportin gain-of-function mutations (ferroportin not down- regulated by hepcidin): 1. Iron uptake in duodenal enterocytes increased

Prevalent in African populations

Pietrangelo. Hematologica 2017

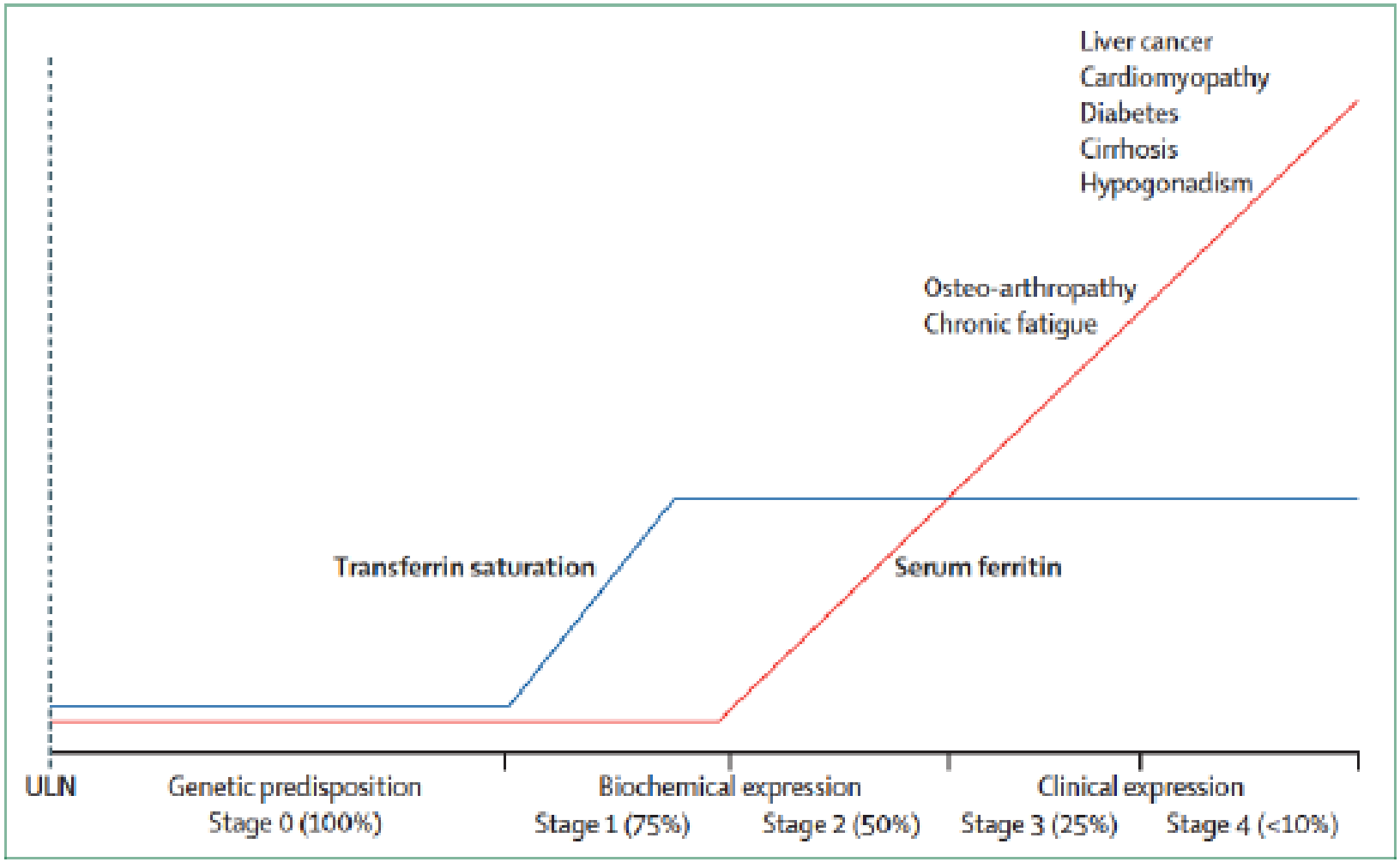
MRI for iron overload





Brissot et al. Nat Rev Dis Primers 2018

Long asymptomatic phase



Powel et al. Lancet 2016

Treatment of hemochromatosis

Phlebotomies (450 mL 1x/week)

Check Hemoglobin 1x/month (no decrease > 20%)

Check Ferritin level every 2 months

Joint pains does not improve may worsen

Reach 1x Ferritin level below 50 ug/L

Continue Phlebotomies (blood donor 3x/year)

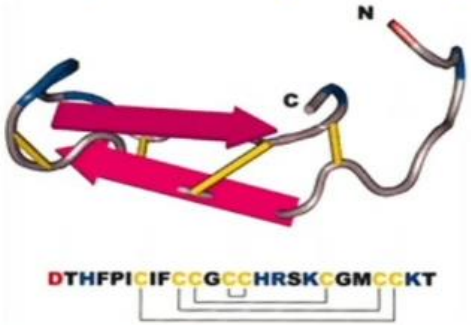
Ferritin 100-200 ug/L

No place for chelators

Treatment of hemochromatosis

Hepcidin Mimetic Rusfertide (also known as PTG-300)

Designed for Superior Drug-like Properties versus Hepcidin



Hepcidin

Natural Hormone and Master Regulator of Iron Homeostasis & Erythropoiesis

- Synthetically complex
  - 25-mer peptide with 4 interlinking disulfide bonds
  - Difficult to synthesize, increased cost
- Stability, solubility, and aggregation challenges
  - Specialized formulations

Rusfertide

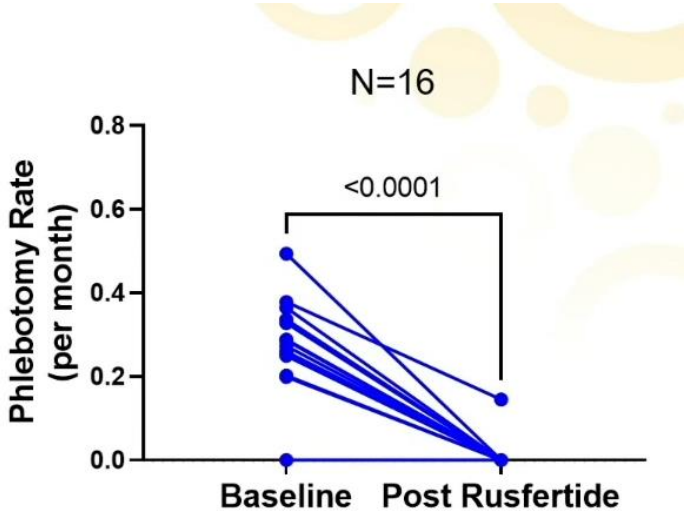
Hepcidin Mimetic: Investigational Therapy for Iron-Related Blood/Tissue Disorders

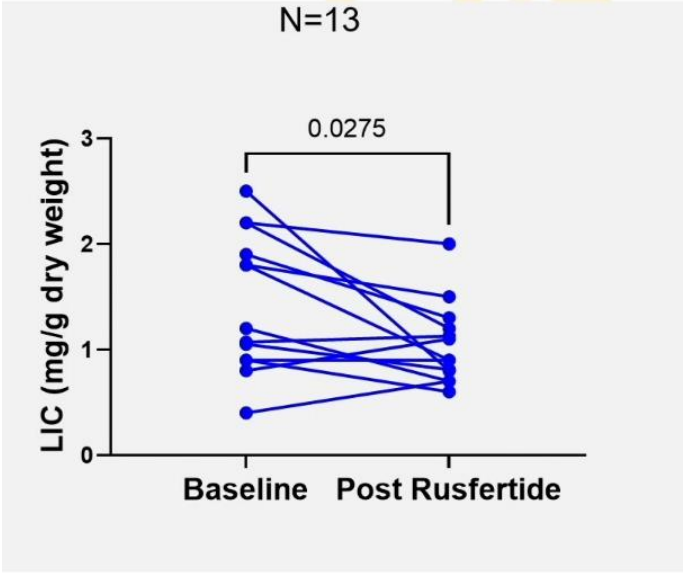
- Designed for superior drug-like properties
  - Potency (*in vitro, in vivo*), PK, solubility, stability (storage)
  - 18-mer peptide with 1 disulfide bond, easier synthesis
- In Phase 2 clinical investigation for
  - Polycythemia vera (PV)
  - Hereditary hemochromatosis (HH)

Kowdley et al. AASLD 2021

Treatment of hemochromatosis

Phase 2 open label in 16 subjects with prior history of HH
In maintenance phase of iron depletion
Administered subcutaneously 1x or 2x per week





Kowdley et al. AASLD 2021

Dietary advices

Avoid medicinal iron

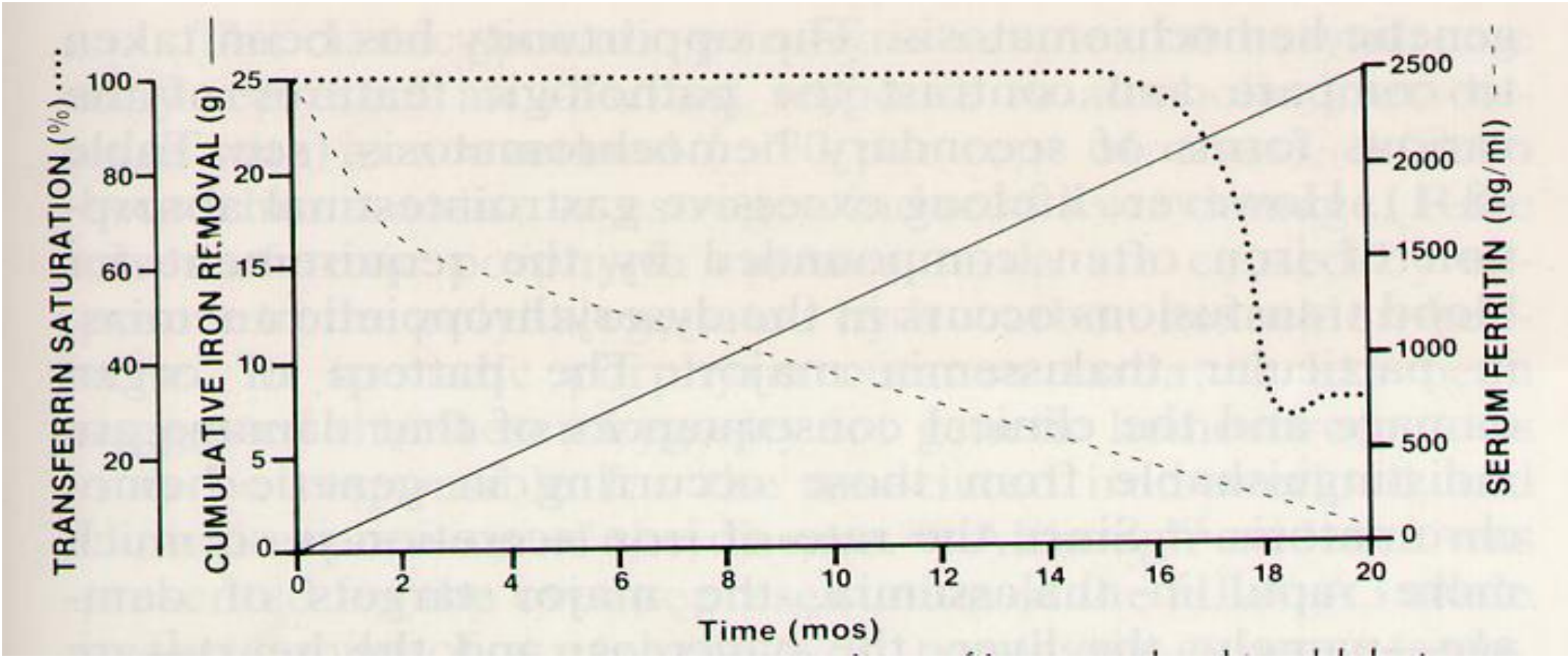
Avoid mineral supplements

Avoid excess vitamin C

Avoid uncooked seafoods (Vibrio vulnificus)

Tea consumption, PPI decrease intestinal iron absorption

Response to phlebotomies



Conclusions

Le fer est essentiel pour notre organisme

Son métabolisme est complexe et implique plusieurs protéines

Seul l‘absorption intestinale est régulée

Trop peu, carence martiale fréquente

Excès pas rare en Europe, génétique