Emocromatosi idiopatica: aspetti diagnostici e terapeutici

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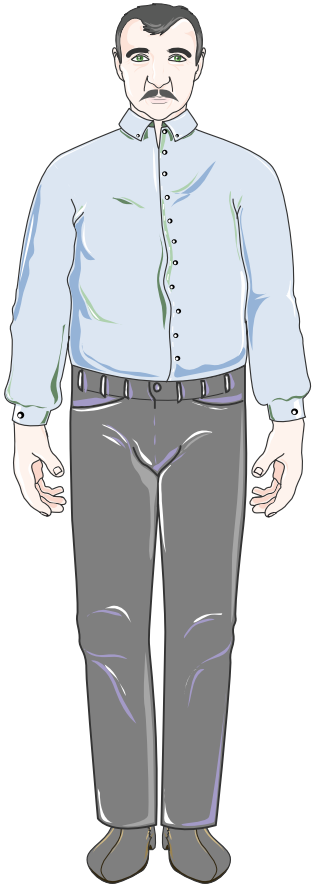
Disclosures of Domenico Girelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
CSL BEHRING						x	
VIFOR PHARMA						x	
NOVO NORDISK						x	
KEDRION PHARMACOSMOS						x	
SANOFI						x	

Agenda

- ✓Clinical case with hyperferritinemia (differential diagnosis).
- ✓Pathophysiology, diagnosis, and management of HFE hemochromatosis.

Clinical case

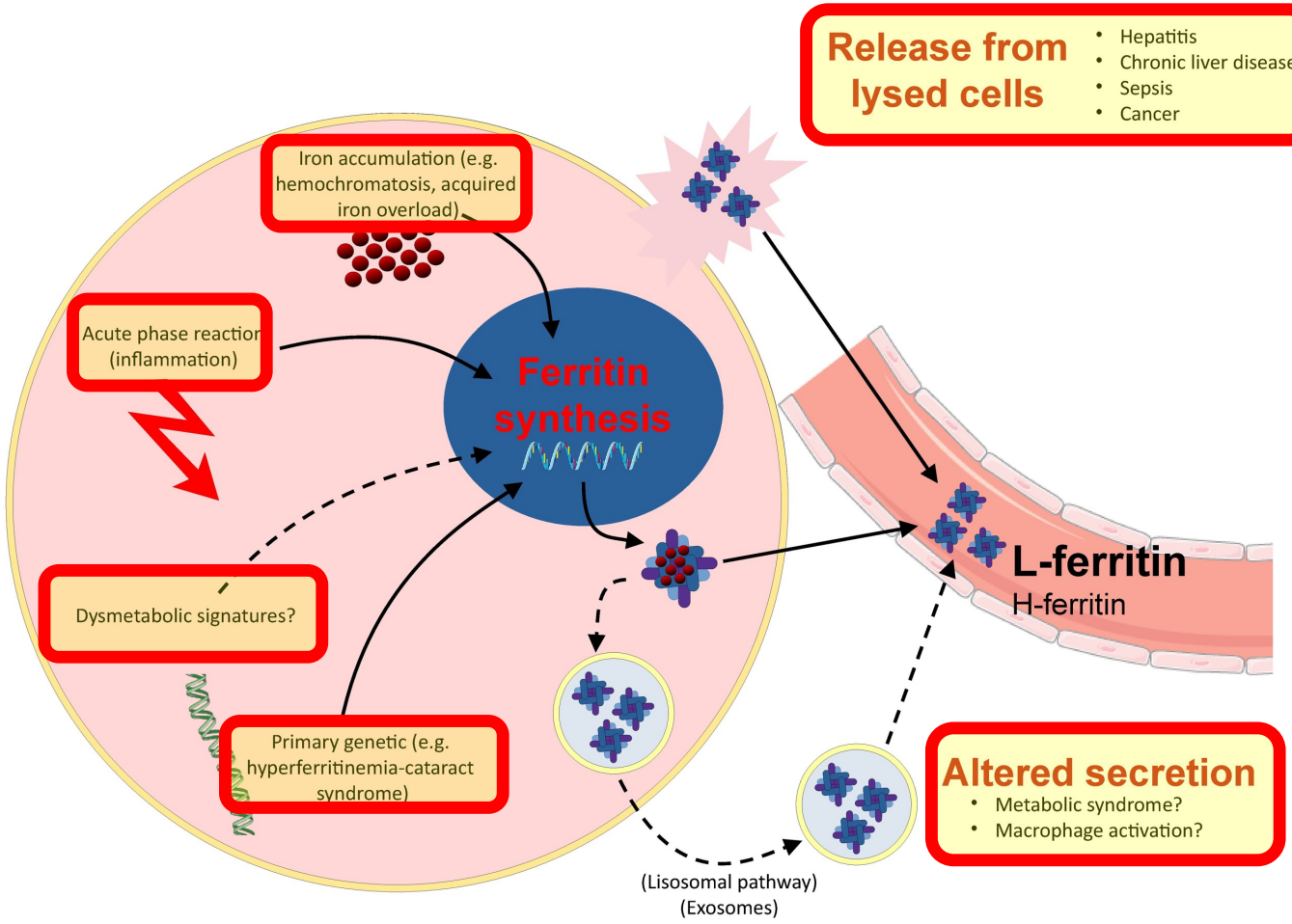


- 56 y Caucasian, asymptomatic
- Family/Past history: unremarkable. No drugs.
- Sedentary (BMI 25.3 Kg/m^2), moderate alcohol intake (1-2 drinks/day).
- Physical Exam: mild hepatomegaly.

- Normal CBC (Hb 15.9 g/dl, MCV 98 fl), CRP, AST, ALT, albumin, glucose, and PT-INR.
- ↑↑ Ferritin (815 μg/L)*

➢ Does he have an iron overload disorder (hemochromatosis)?

Mechanisms leading to hyperferritinemia



Ferritin is an **intra**cellular protein!
Few amount (μg/L) secreted by the lysosomal pathway

Girelli D, Adv Exp Med Biol 2025.

Differential Diagnosis of Hyperferritinemia*.

Clinical history

Key questions:

- ✓ Why ferritin was ordered?
- ✓ Family history of hyperferritinemia, iron overload, liver or hematological diseases, early cataracts?
- ✓ Risk factors for liver disease?
- ✓ Alcohol intake (current/past)?
- ✓ Previous blood transfusions or iron therapies?
- ✓ Chronic inflammatory disorders or recent acute illness?
- ✓ Lifestyle risk factors, dysmetabolic features or MAFLD?

n.1

Conditions associated with hyperferritinemia	TSAT
Metabolic Hyperferritinemia Pts. with dysmetabolic features (obesity, hypertension, dyslipidemia, diabetes m., liver steatosis).	N
Inflammatory diseases Infections (e.g., sepsis, COVID-19), autoimmune disorders, malignancies.	N or ↓
Rare genetic disorders Gaucher disease Hyperferritinemia-cataracts syndrome Aceruloplasminemia	N
Hemochromatosis (*HFE* and non-*HFE*)	High
Hepcidin deficiency from other causes Liver cirrhosis (whatever the etiology), alcohol abuse, ineffective erythropoiesis	High
Iatrogenic iron overload Repeated blood transfusions and/or prolonged iron therapy (especially IV)	High
Liver cytolysis Chronic or acute hepatitis, Hepatocellular carcinoma	Variable

*<10% of pts. have an IO disorder

- ❖ TSAT
- ❖ CBC
- ❖ C-reactive protein
- ❖ Liver function test
- ❖ Glucose and plasma lipids

Metabolic Hyperferritinemia:
TSAT N and dysmetabolic features.

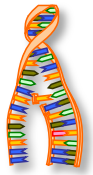
Normal TSAT generally excludes Hemochromatosis, which, on the other hand, need to be considered whenever TSAT is increased

Girelli D, Hematology Am Soc Hematol Educ Program 2024

What is hemochromatosis (and what is not)

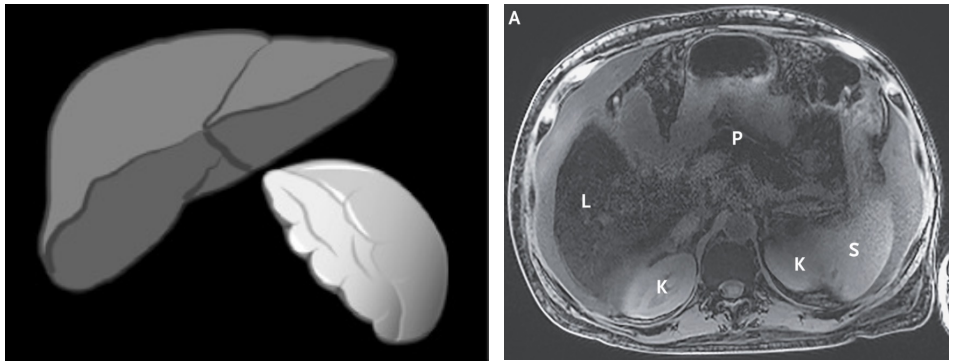
The term should be **reserved** for:

- A **distinct genetic disease** due to **mutations** leading to **insufficient hepcidin production** (very rarely to ↓ activity) and ↑ **iron absorption**.

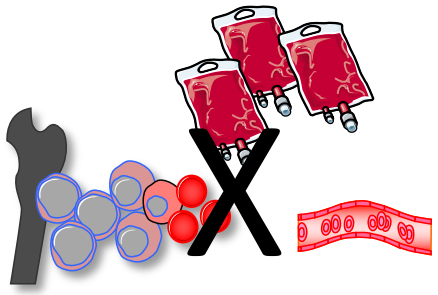


- Characterized by ↑↑ **TSAT (>45%)**, ↑ ferritin, and **progressive accumulation of toxic iron** forms (confirmed by **MRI** ± liver biopsy)…

- … and by the **absence of signs of a primary RBC disorder** (≠ from transfusional IO and iron-loading anemias)



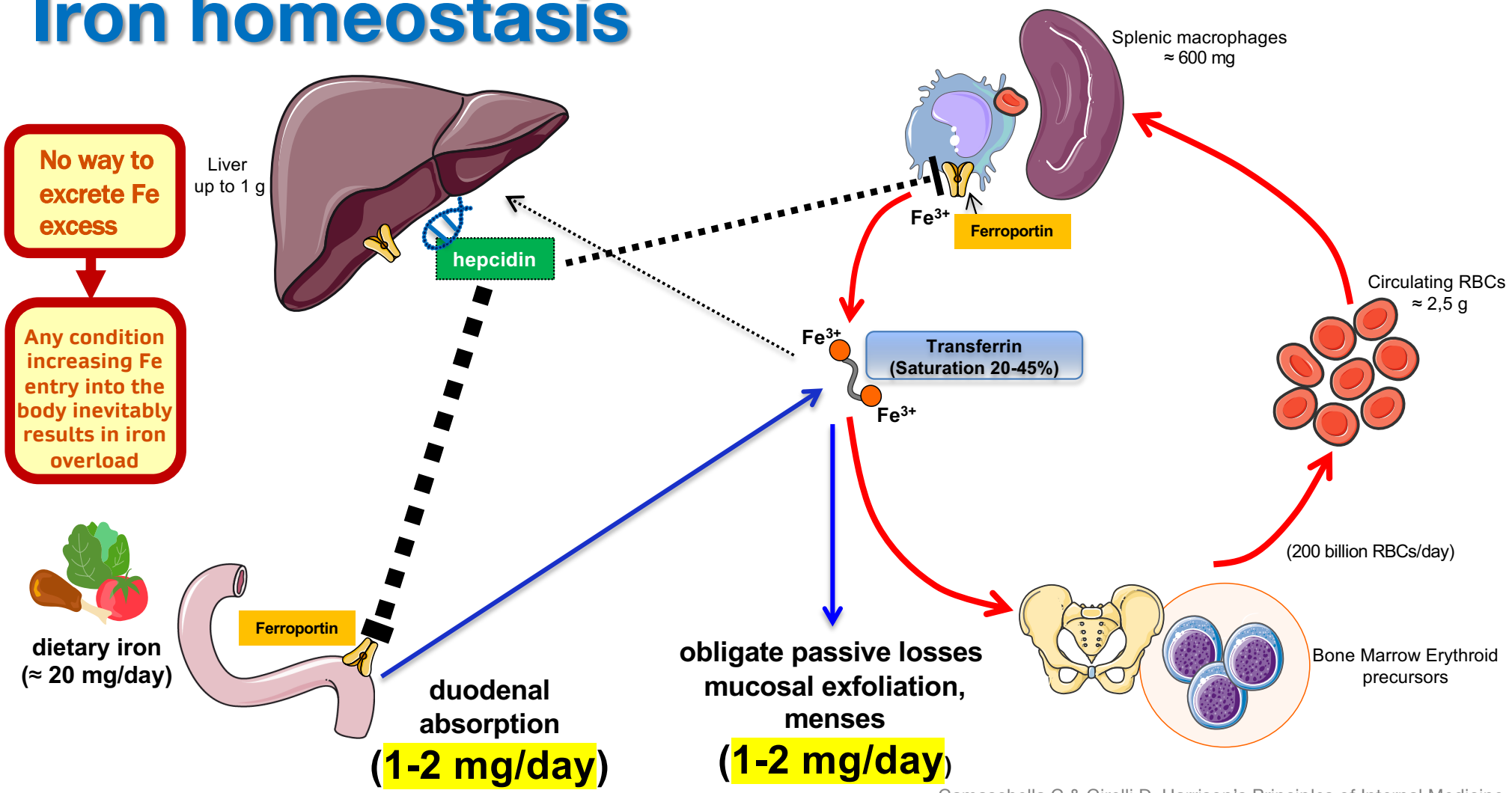
"Black liver and white spleen pattern"
Signal loss in T1-weighted-images due to ferrimagnetic iron



No anemia or reticulocytosis
Ineffective erythropoiesis
Transfusions

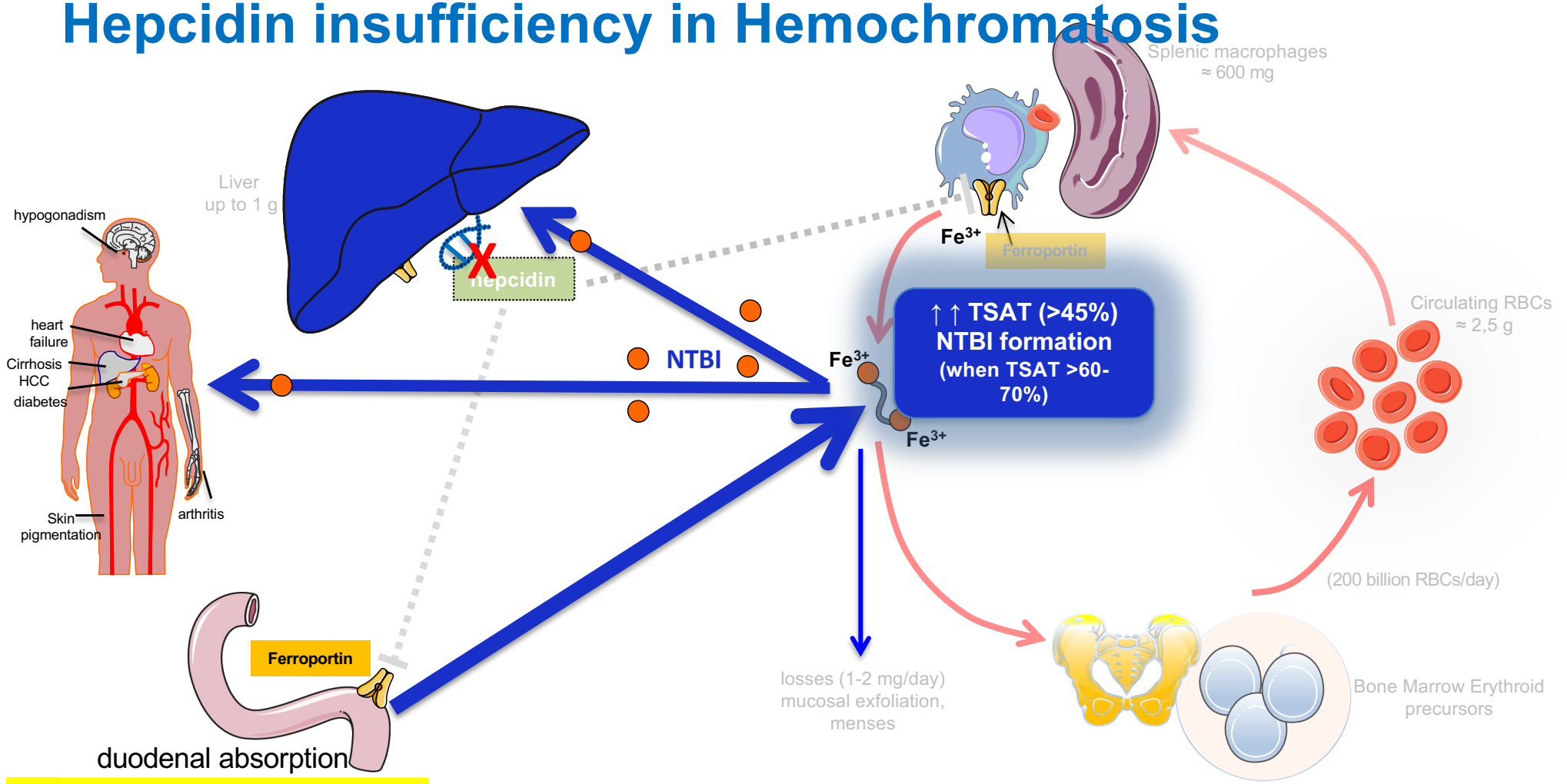
Brissot P, Pietrangelo A, Adams PC et al. Nat Rev Dis Primers 2018 Apr 5:4:18016.
Girelli D, Busti F, Brissot P, at al. Blood 2022; 139:3018.
Olynyk J & Ramm GA. N Engl J Med 2022; 387:2159.
Adams PC, Jeffrey G, Ryan J. Lancet 2023; 401:1811.

Iron homeostasis



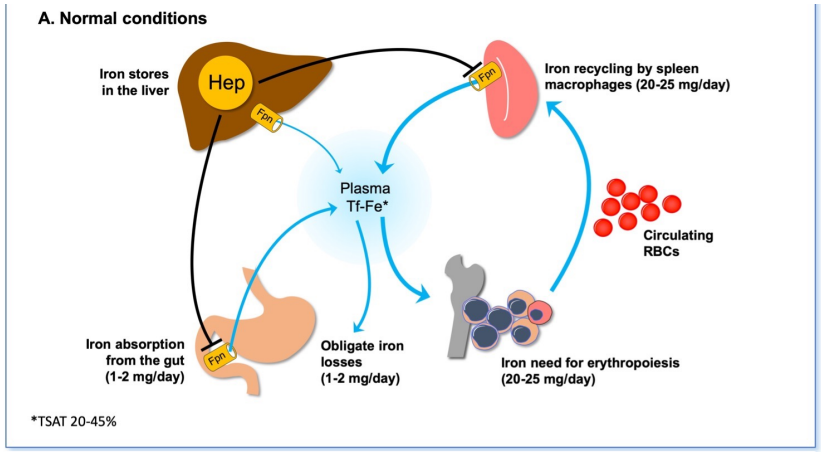
Camaschella C & Girelli D, Harrison's Principles of Internal Medicine, 22nd Ed. 2025.

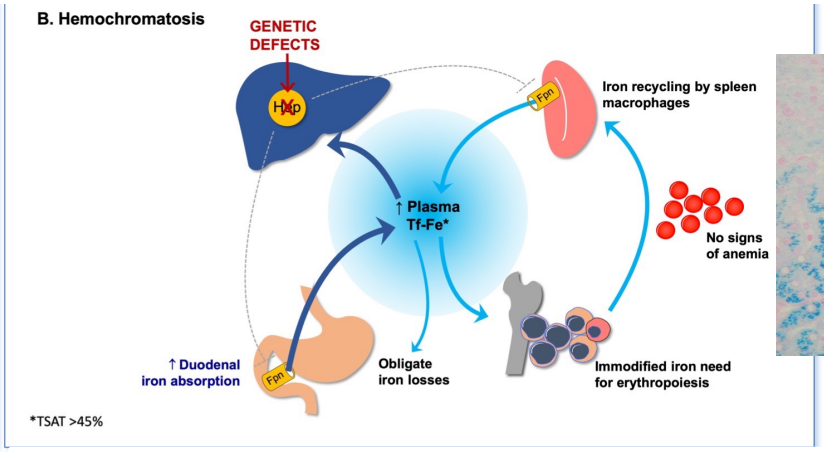
Hepcidin insufficiency in Hemochromatosis

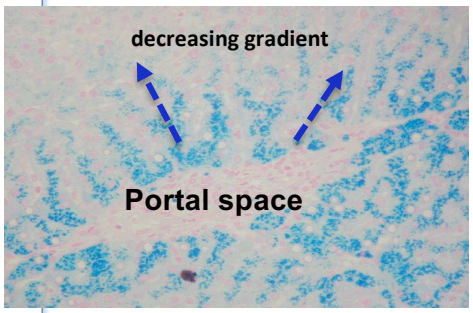


Adapted from Camaschella C & Girelli D, Harrison's Principles of Internal Medicine, 22nd Ed. 2025.

Different pathophysiology of IO disorders



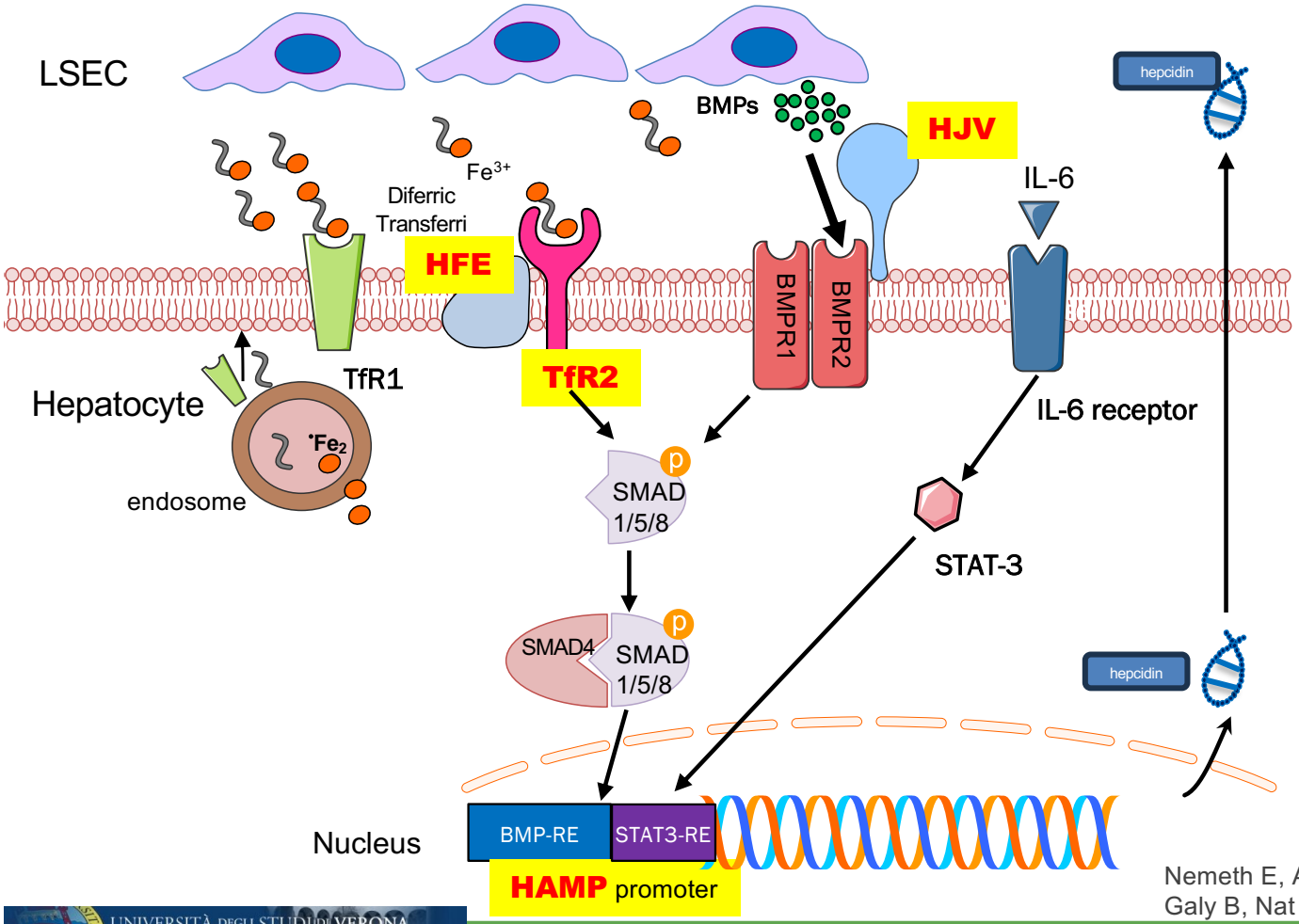




Liver biopsy (Perls' staining)

Girelli D, Busti F, Brissot P, at al. Blood 2022; 139:3018.

Hemochromatosis: a genetically heterogeneous disorder



Mutations in at least 5 genes encoding different **upstream regulators of the positive feedback response of hepcidin to iron:**

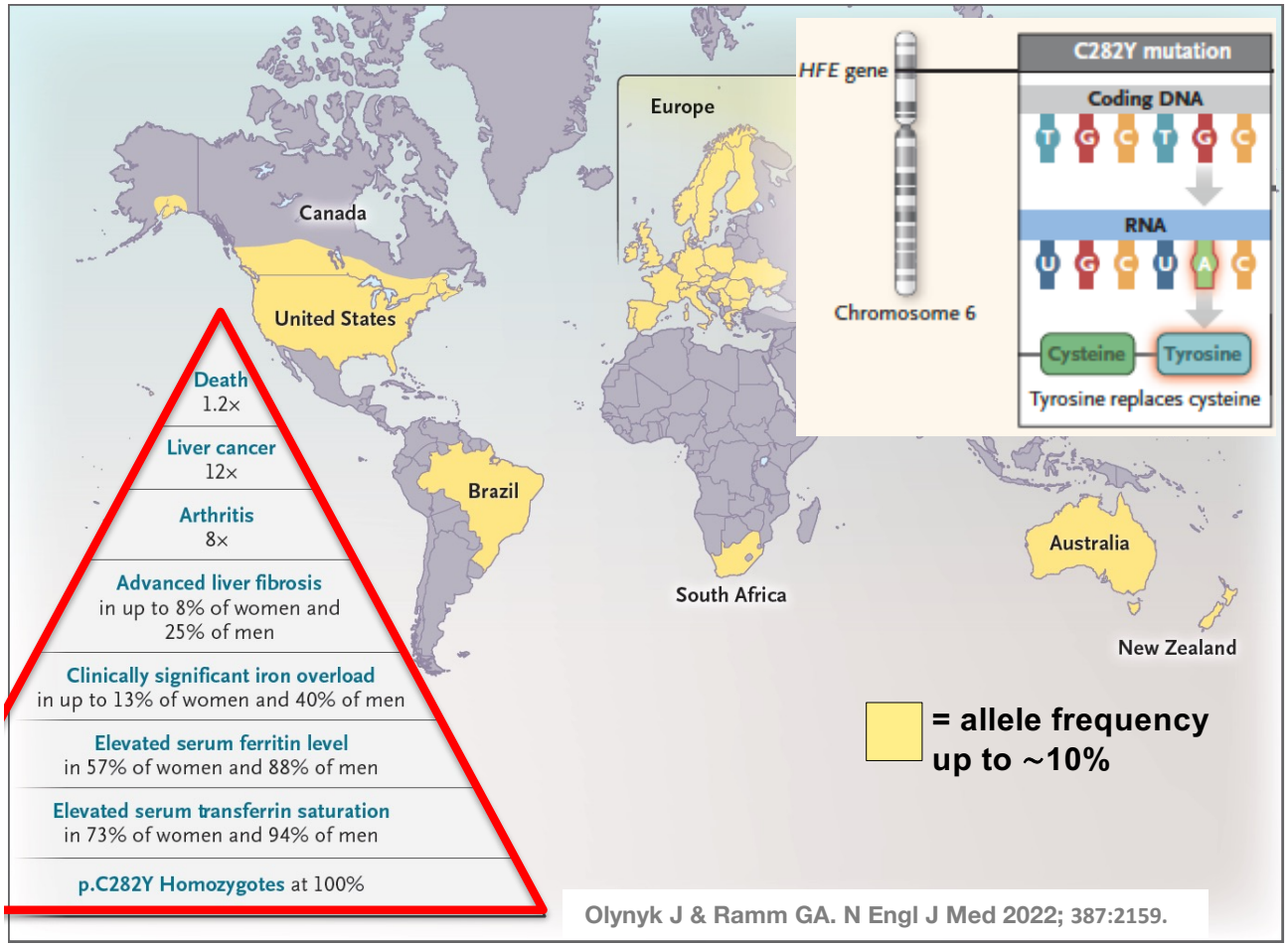
- **HFE C282Y +/+ (most cases)**

Rare/very rare

- **TFR2 (Transferrin Receptor 2=**
- **HJV (Hemojuvelin)**
- **HAMP (hepcidin)**
- **SLC40A1 (ferroportin):** when gain-of-function mutations lead to hepcidin resistance

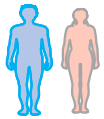
Nemeth E, Annu Rev Med 2023;74:261.
Galy B, Nat Rev Mol Cell Biol 2024;25:133.

Global prevalence of the HFE p.C282Y allele and spectrum of expression



Olynyk J & Ramm GA. N Engl J Med 2022; 387:2159.

Low penetrance

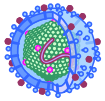


M present in the V decade
F protected by Fe losses with menses

Penetrance increased by:
Acquired cofactors that further inhibit hepcidin

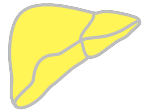
- **Alcohol**

- **hepatitis C virus**



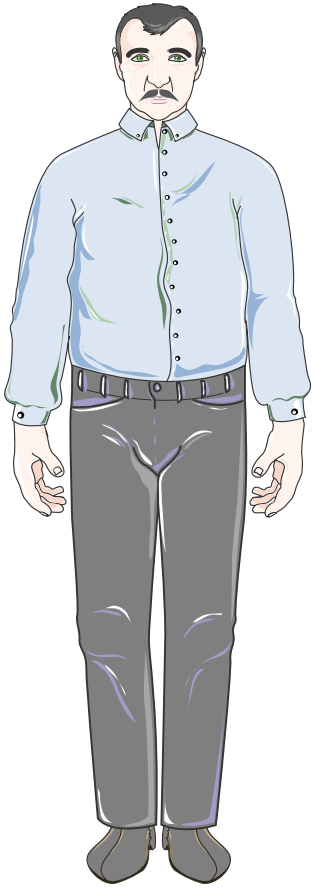
or by:

- **other causes of liver morbidity, esp. metabolic-associated fatty liver disease (MAFLD)**



Girelli D, Hematology Am Soc Hematol Educ Program 2024

Clinical case



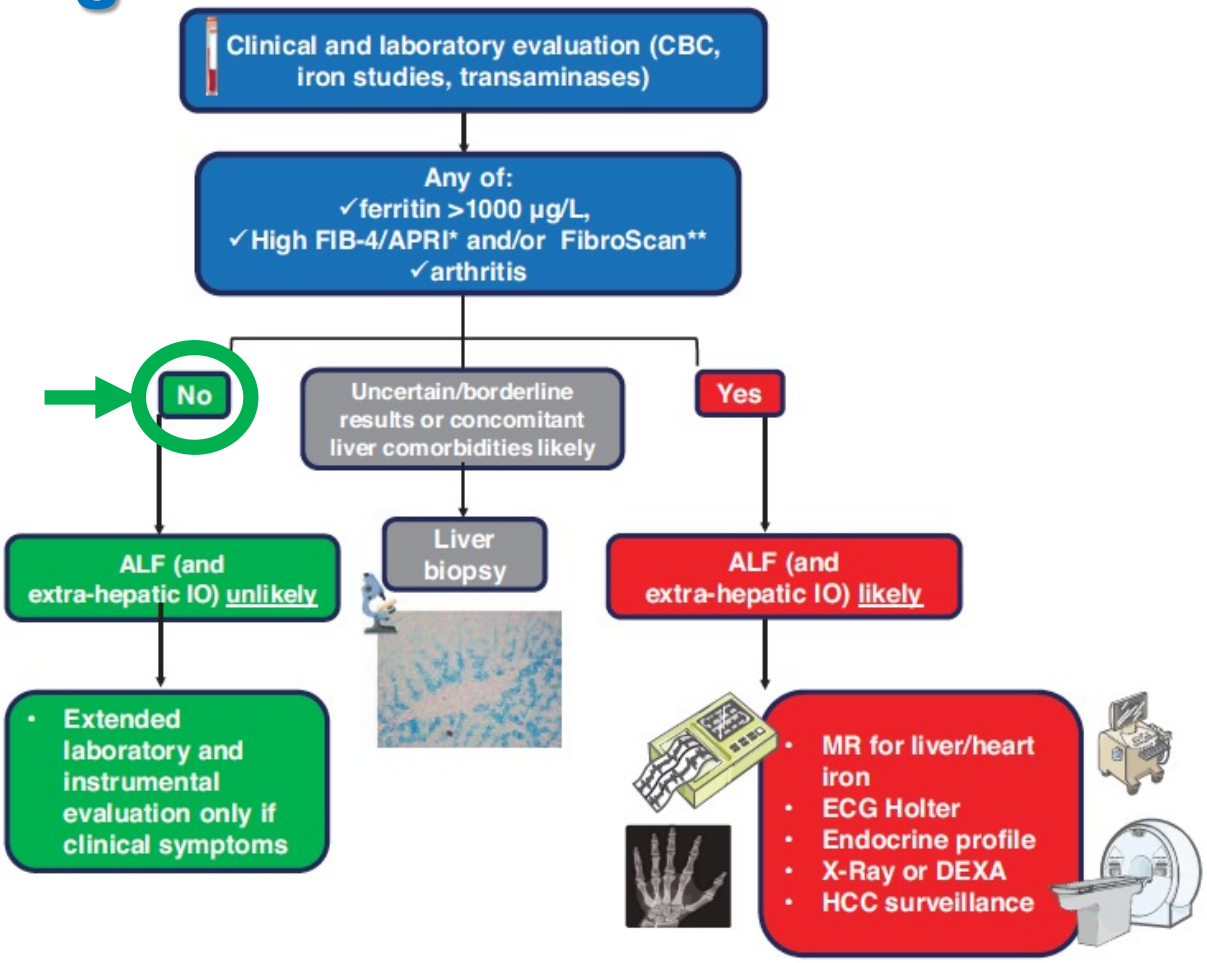
- 56 y Caucasian, asymptomatic.
- Family/Past history: unremarkable. No drugs.
- Sedentary (BMI 25.3 Kg/m^2), moderate alcohol intake (1-2 drinks/day).
- Physical Exam: mild hepatomegaly.

- Normal CBC (Hb 15.9 g/dl, MCV 98 fl), CRP, AST, ALT, albumin, glucose, and PT-INR.
- ↑↑ Ferritin (815 μg/L)*

➢ TSAT 88%

➢ C282Y +/+

Staging of Hemochromatosis



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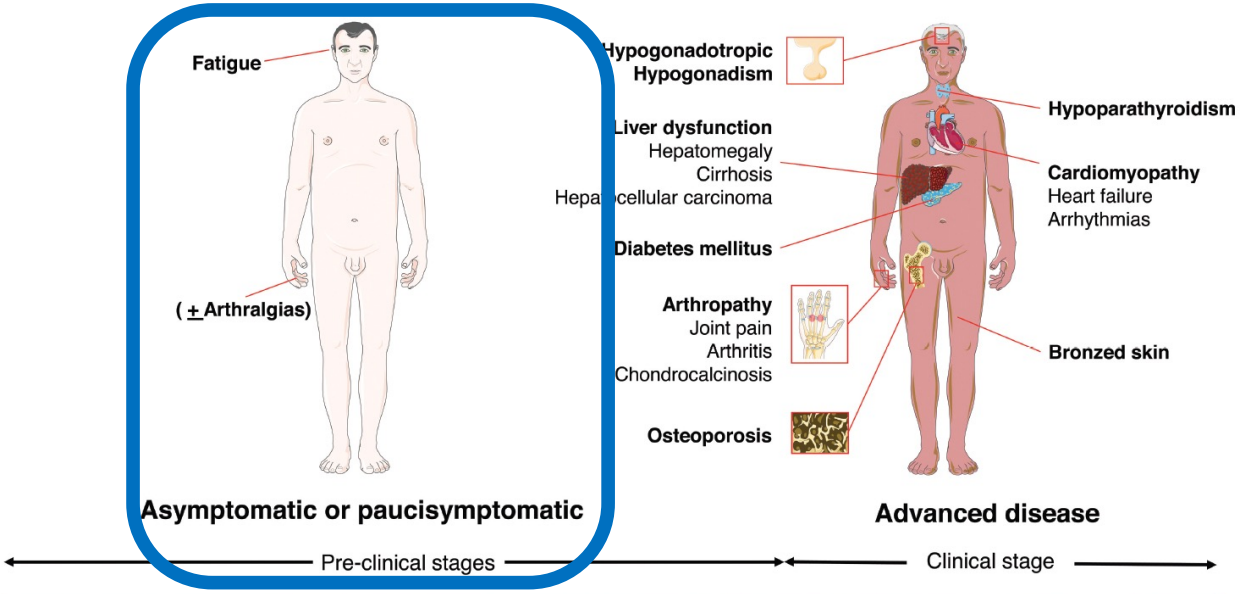
Clinical spectrum of HFE-Hemochromatosis



Genetic predisposition	Biochemical expression ± mild symptoms	Overt disease
Low penetrance of the classical *HFE C282Y* +/+ genotype	↑ TSAT (>45-50%) is firstly altered (from the 2nd – 3rd decade). Then, ferritin also progressively increases. Early symptoms can be fatigue or arthralgias. Severe symptoms usually do not appear until ferritin is >800-1000 µg/L.	Multi-organ damage due to severe IO. This stage is associated with ↓↓ QoL. Life-expectancy may be also reduced.

Protective Factors

Female gender
(Menses, pregnancies, breastfeeding)
Regular blood donations
Genetic factors (?)

Risk Factors

Inadequate lifestyle favoring MAFLD
Other chronic liver disease (e.g., HCV)
Alcohol abuse
Ineffective erythropoiesis/chronic hemolysis
Blood transfusions
Inappropriate iron therapy
Genetic factors (polygenic risk scores)

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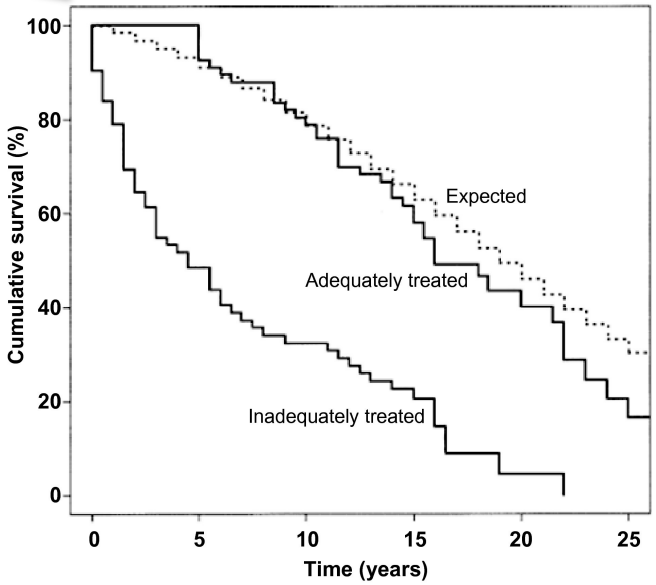
Phlebotomy in hemochromatosis (standard of care)

- Safe, cheap, well-tolerated.
- ↓↓ morbidity and mortality when started before cirrhosis and/or diabetes.
- Disadvantages: "invasive", needs attendance at a health-care facility. Arthropathy may not ameliorate (even worsen).

Recommendations

Phlebotomy encompasses an induction and maintenance phase. During the induction phase, phlebotomy should be performed weekly (or fortnightly) until iron stores are depleted. The target for iron depletion during induction is a serum ferritin of 50 µg/L, but not lower to avoid iron deficiency **(LoE 4, strong recommendation, strong consensus).**

In the maintenance phase, serum ferritin can be maintained with some flexibility in the range of 50-100 µg/L



Note:

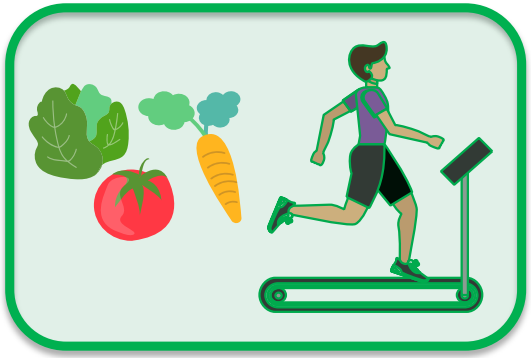
- iron deficiency should be avoided (further suppresses hepcidin)

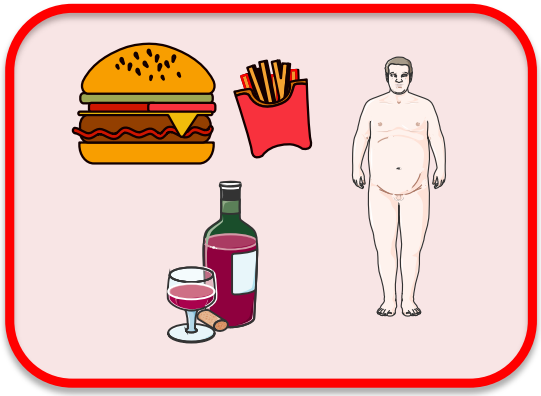
Prabhu A, Cargill T, Roberts N, Ryan JD. Hepatology 2020;72:1469.
European Association for the Study of the Liver (Zoller H et al). J Hepatol 2022;77:479.

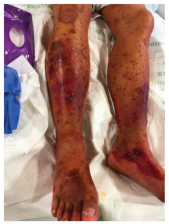
Lifestyle modifications in H

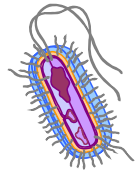
*to minimize **factors influencing the clinical penetrance** of H by **further suppressing hepcidin** (e.g., **alcohol**) and/or promoting **liver injury** (e.g., **steatosis**)*

- Minimize or avoid alcohol
- Healthy diet (red meat not strictly prohibited, but the lower, the better)
- Avoid vitamin C and iron (in “multivitamin” supplements)
- Regular physical activity
- Maintain ideal weight
- Avoid raw or undercooked seafood and wound contact with seawater*.









*Vibrio vulnificus

European Association for the Study of the Liver. J Hepatol 2022;77:479.

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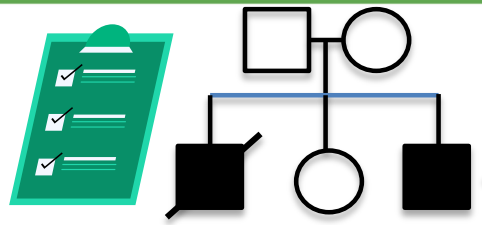
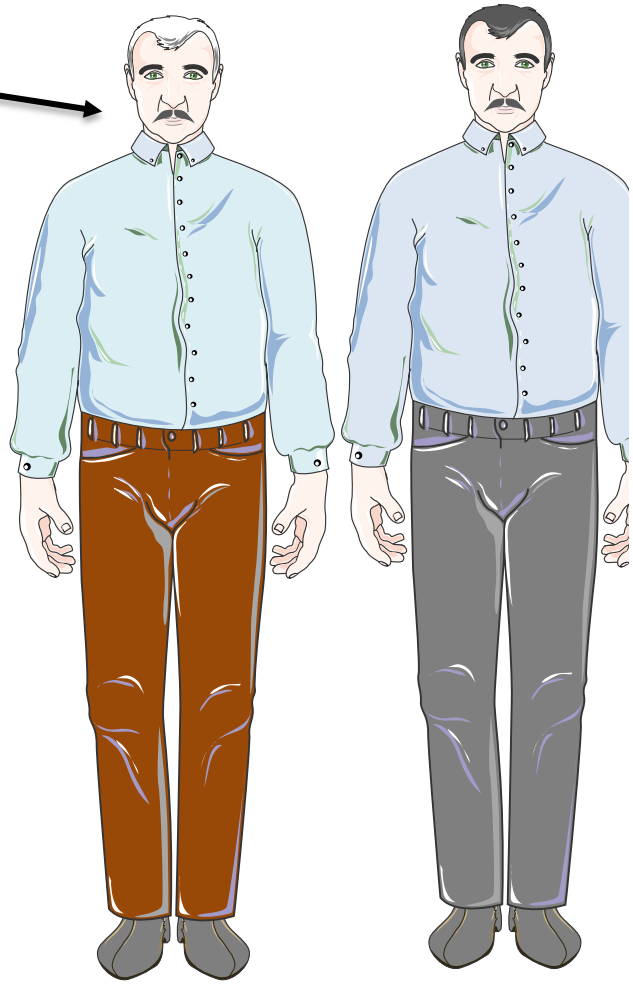
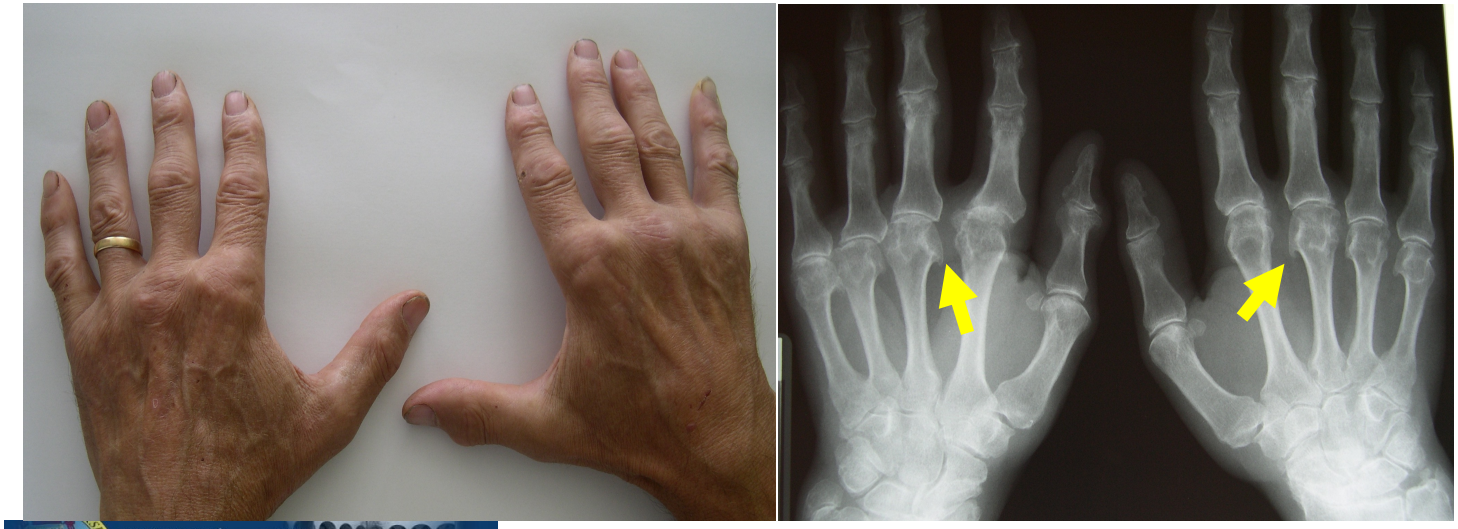
Family screening





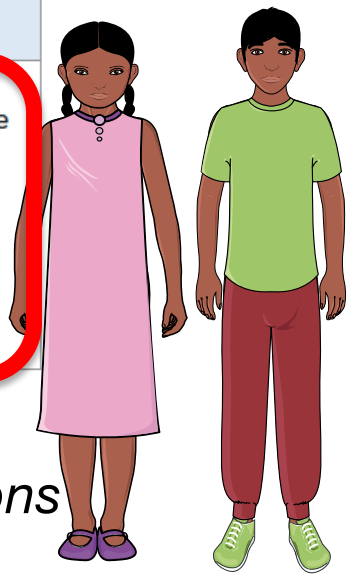
62 y brother: **HFE C282Y +/+**, **ferritin 1020 μg/L, TSAT 78%,** mild ↑ AST/ALT.

- 2 years before: diagnosis of **"seronegative undifferentiated arthritis"** poorly responsive to hydroxychloroquine.
- ALF likely (ferritin < 1000 + arthropathy). No other relevant complications.
- **Phlebotomy**, **surveillance for HCC**, and **physiotherapy**



The simplified BIOIRON classification of H

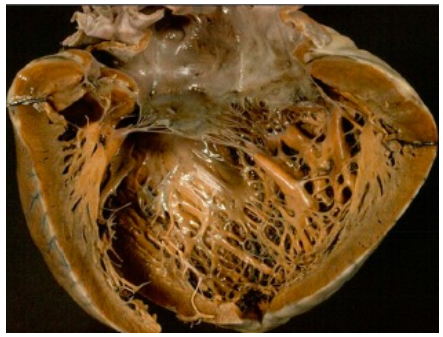
	Gene/mutations	Molecular diagnosis	Clinical features	Pathophysiology
HFE	*HFE* (High Fe)	First-level genetic test for C282Y (widely available)	Common In populations of Northern European descent Low penetrance, often requiring cofactors. Adults, typically after the fourth-sixth decades, predominantly in males	Mild hepcidin deficiency, with blunted feedback response to increasing plasma Fe. Hepcidin level mildly reduced or inappropriately normal for iron stores.
non HFE	*HJV* (hemojuvelin) *HAMP* (hepcidin) *TFR2* (transferrin receptor 2) *SLC40A1* (ferroportin)[a] Digenic inheritance possible (*PIG-A*)[b] (other still unknown)	Second-level genetic test (NGS panel looking for "private" mutations in iron genes) available at referral centers and requiring expert inter-pretation	Rare or ultrarare Any population High penetrance (negligible role for cofactors) Juvenile onset (esp. *HJV* and *HAMP*) Both sexes equally affected Heart and endocrine complications often predominant (esp. *HJV* and *HAMP*)	Severe hepcidin deficiency (or, rarely, hepcidin resistance in gain-of-function *SLC40A1* mutations). Hepcidin levels very low to undetectable (increased in hepcidin resistance).

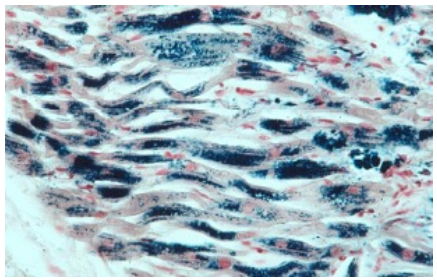


All forms are autosomal recessive, except for dominant ferroportin mutations

Girelli D, Busti F, Brissot P, at al. Blood 2022; 139:3018.
Olynyk J & Ramm GA. Hemochromatosis. N Engl J Med 2022; 387:2159.

Personalized treatment in severe hemochromatosis





Brown myocardium and iron deposits in cardiomyocytes in a pt. with non-HFE (HJV-related) H

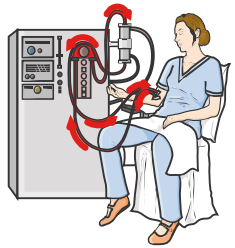
Thiene G, Biology 2025

HEART FAILURE with HEMODYNAMIC INSTABILITY

ENDOCRINE COMPLICATIONS
(e.g., diabetes, hypogonadism)

MISCELLANEOUS
Osteoporosis, severe arthropathy, anemia (rare)

ERYTHROCYTAPHERESIS
(isovolemic procedure)



IRON CHELATORS
DFO s.c. 25-40 mg/kg 5-7 days/week.
Oral chelators can be used but off-label.

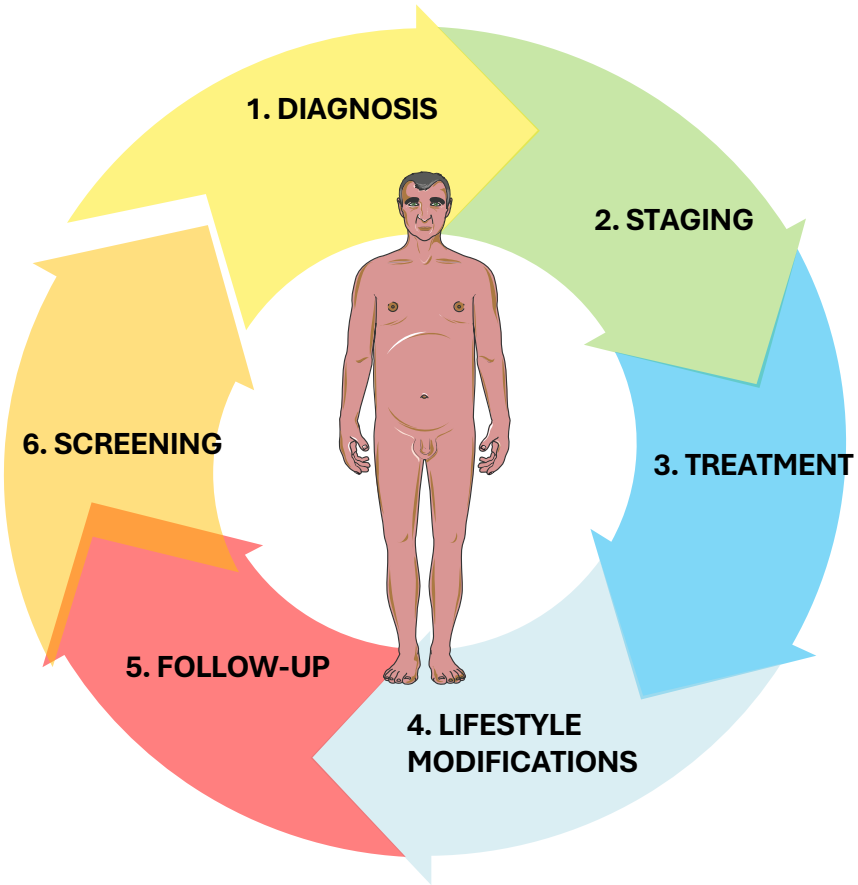
HORMONE REPLACEMENT
(e.g. insulin, androgens)

OTHER PHARMACOLOGICAL Rx
(e.g. bisphosphonates, anti-arthritis)
Hepcidin agonists (?)

"LOW INTENSITY" PHLEBOTOMIES
(e.g. 150-200 ml at close intervals)

European Association for the Study of the Liver. J Hepatol 2022;77:479.

SUMMARY: COMPREHENSIVE MANAGEMENT OF HEMOCHROMATOSIS



1. DIAGNOSIS

- ✓ ↑ TSAT (hallmark)
- ✓ ↑↑ Ferritin
- ✓ *HFE* C282Y test
- ✓ NGS (non-HFE-H)

2. STAGING

- ✓ FIB-4
- ✓ FibroScan
- ✓ MR
- (Liver biopsy)

3. TREATMENT (IRON DEPLETION)

- ✓ Phlebotomy
- ✓ Erythrocytapheresis
- ✓ (Iron chelating agents

4. LIFESTYLE MODIFICATIONS

- ✓ Healthy diet
- ✓ Regular exercise
- ✓ No or ↓ Alcohol

5. FOLLOW-UP

- ✓ Maintenance phlebotomy or blood donation
- ✓ HCC surveillance (selected cases)

6. SCREENING

- ✓ 1st degree relatives

Girelli D, Marchi G, and Busti F. Hematology 2024

LIGHTS IN EMATOLOGIA

GIMFer
AOUI VERONA
GRUPPO INTERDISCIPLINARE MALATTIE DEL FERRO

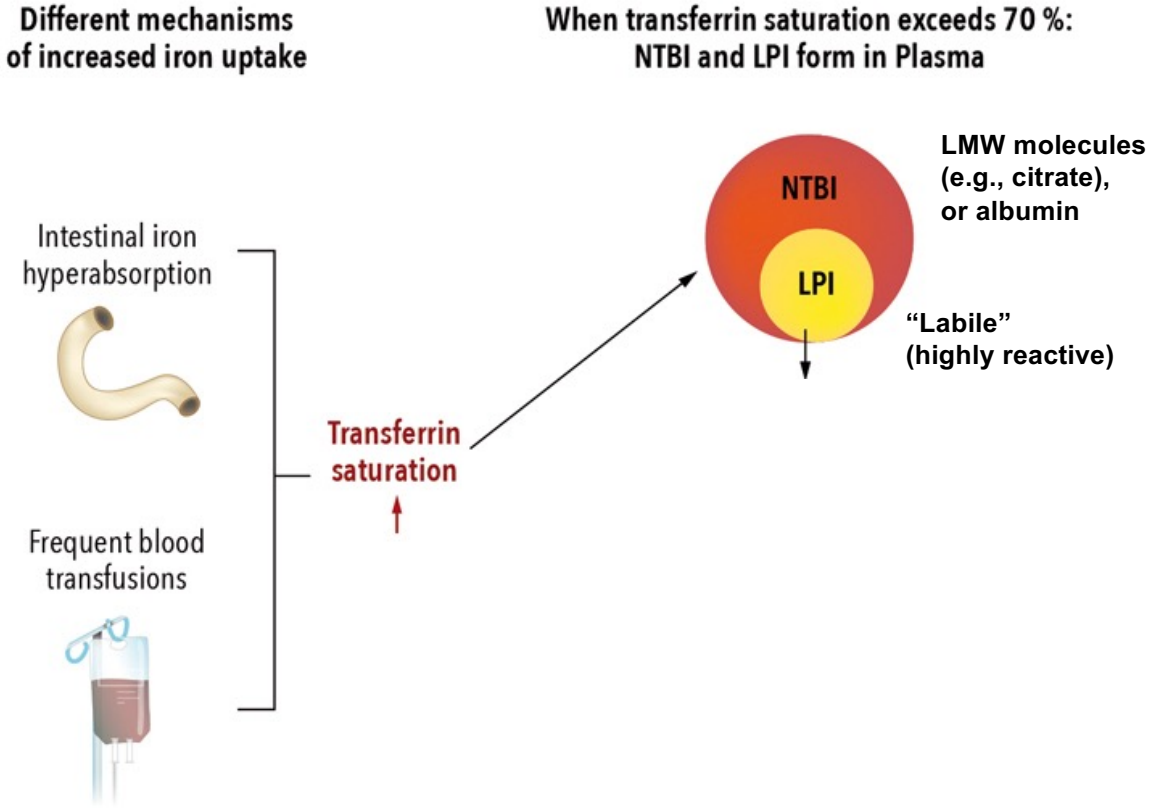
European Reference Network

UNIVERSITÀ DEGLI STUDI DI VERONA

Verona Interdisciplinary Group on Iron Disorders

Thanks for lifelong mentorship

The central role of Non-Transferrin Bound Iron (NTBI)



Brissot P, Nat Rev Dis Primers 2018
Rüfer A, Swiss Med Wkly 2017