Thursdays Webinars

EuroBloodNet

Challenges in the management of HFE-related hemochromatosis

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ERN-EuroBloodNet subnetwork: **Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis**
Porto – Portugal
19 March 2020

Co-funded by the Health Programme of the European Union

European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

My disclosures

Advisory Boards of :

VIFOR

SILENCE THERAPEUTICS

Invited Speaker for :

NOVARTIS

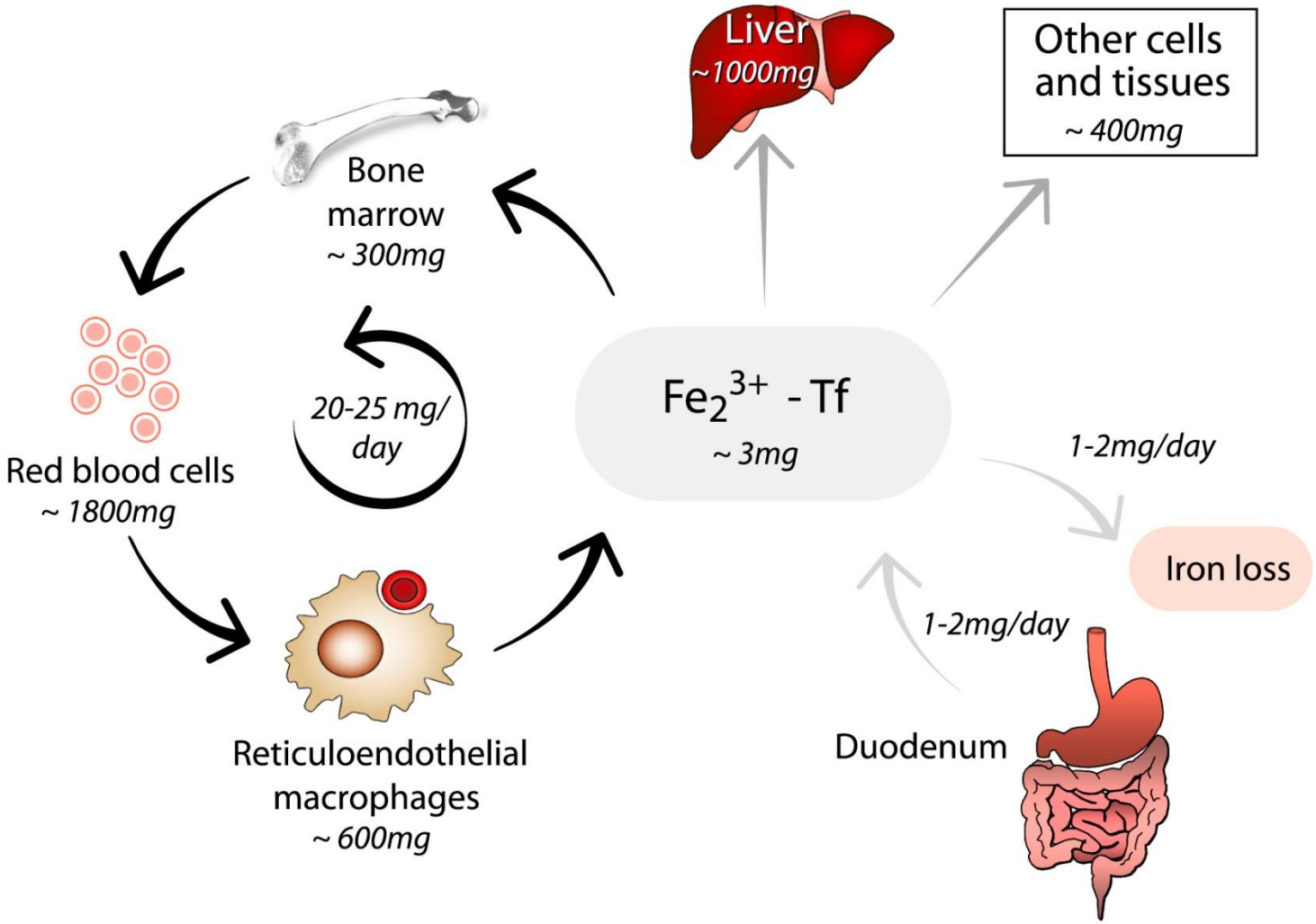
Learning objectives:

1. To understand the etiopathogenesis of Hemochromatosis

2. To know how to act in practice to suspect, diagnose and treat HFE related hemochromatosis

3. To discuss the best screening strategies for disease prevention

THE SYSTEMIC IRON HOMEOSTASIS



Hentze, Muckenthaler and Andrews, Cell (2004)

THE SYSTEMIC IRON HOMEOSTASIS

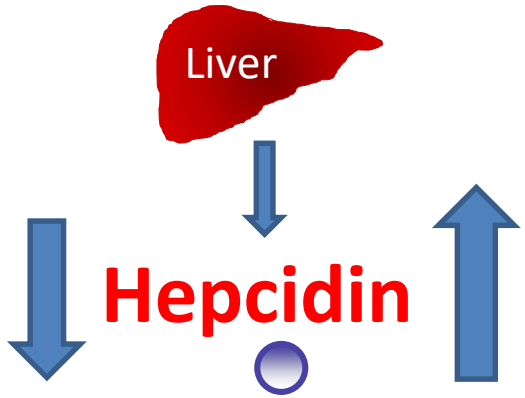
REGULATION DEPENDENT ON FACILITATING OR LIMITING IRON ENTRY INTO CIRCULATION!!!!

DOWN regulators:

Iron Deficiency

Hypoxia

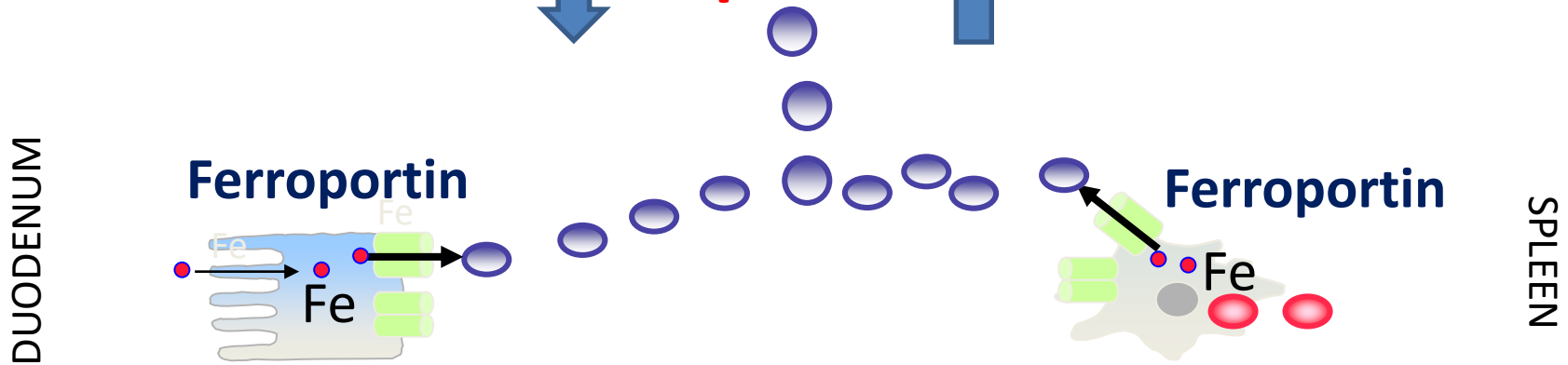
↑Erythroid activity



UP regulators:

Iron Overload

Inflammation



European Reference Network for rare or low prevalence complex diseases

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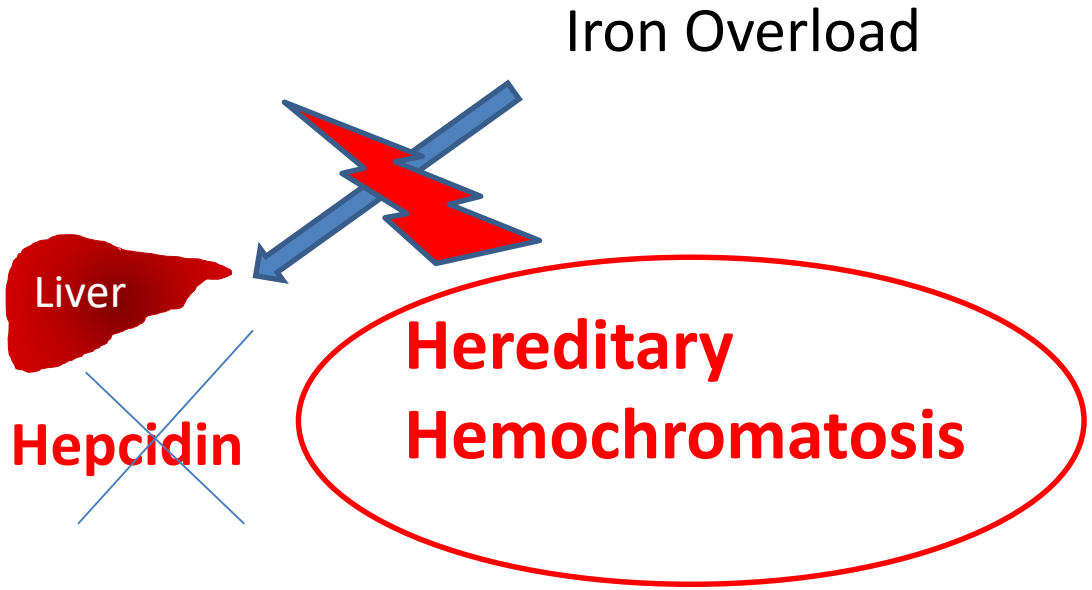
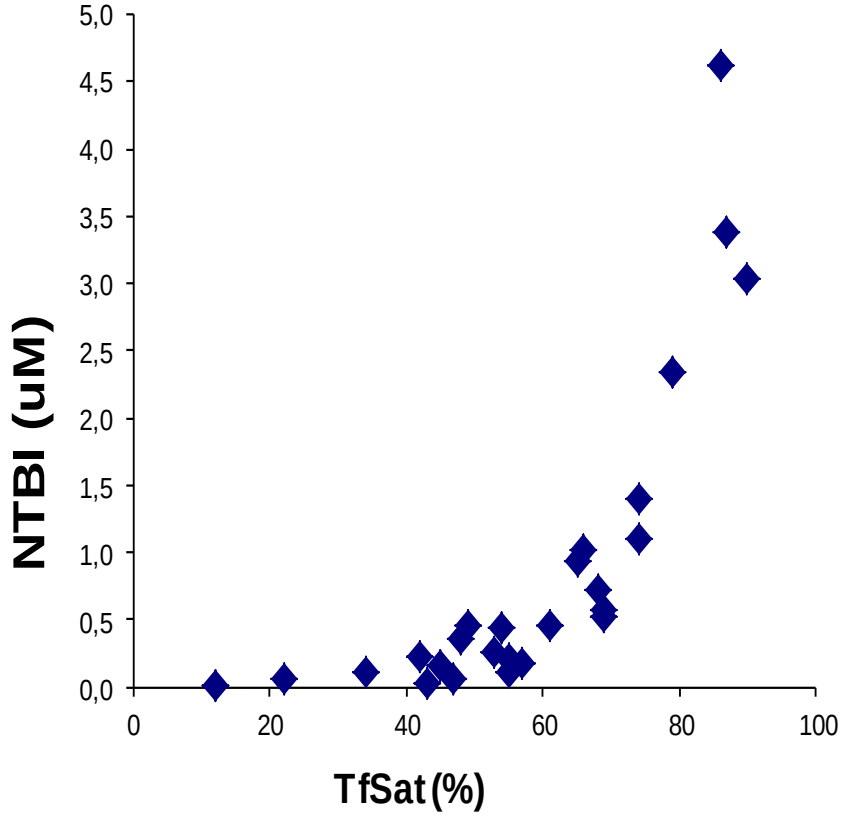
IRON "SENSING" AND HEPCIDIN SIGNALING "FAILS" IN HH



↑ Iron Absorption

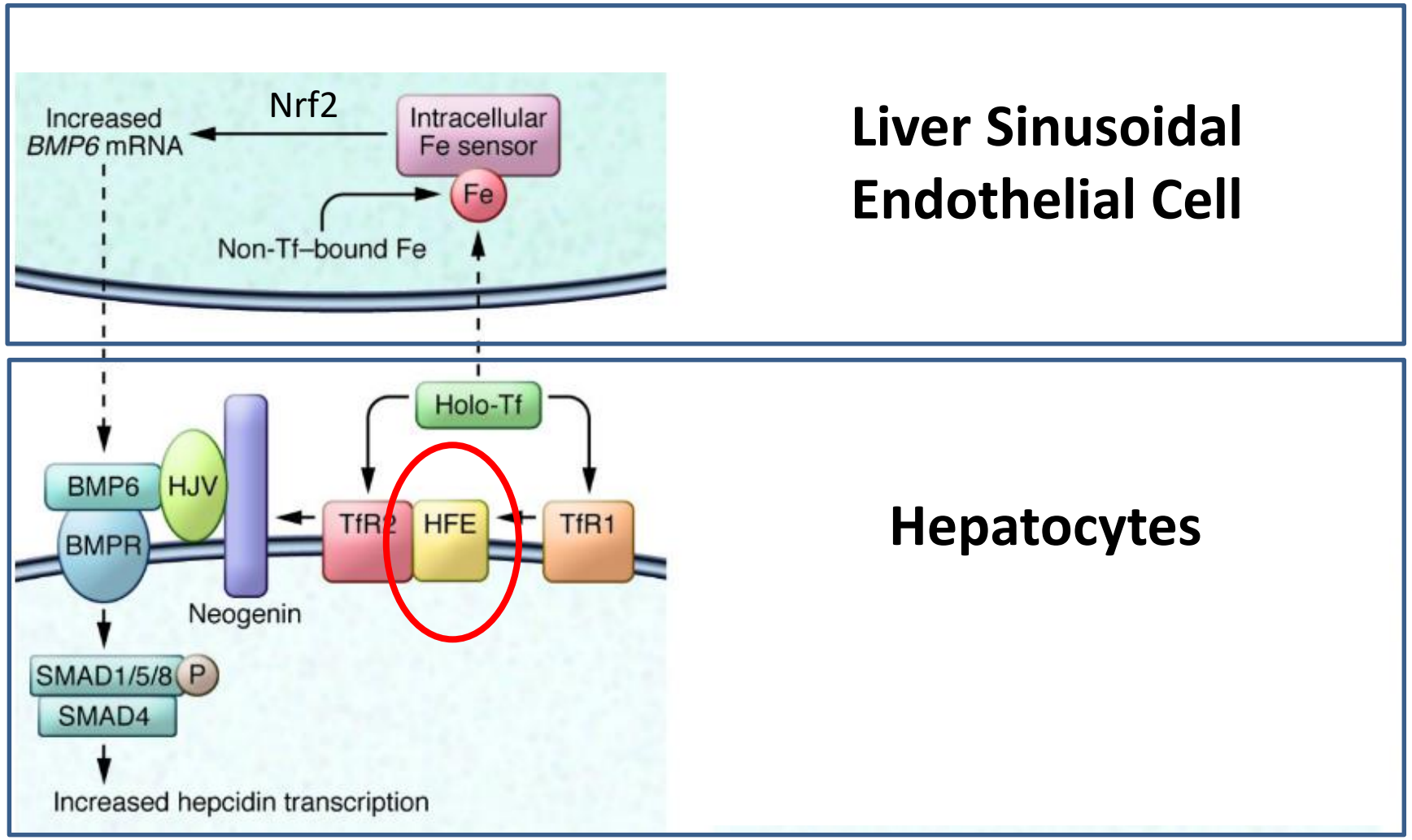
↓Machrophage retention

↑Fe-Tf



Data from: *Silva A & Porto G (2016)*

IRON "SENSING" AND HEPCIDIN SIGNALING IN THE LIVER



Adapted From: Zhau et al. J Clin Invest. 2013;123(6):2337-2343

HH DEFINITION

Hepcidin deficiency causes increased transferrin saturation, which is the unifying feature and principal biochemical finding of **all forms of HH**

Nat Rev Dis Primers. 2018 Apr 5;4:18016

DIAGNOSTIC CRITERIA: (1st Suspect!)

1st line Biomarkers of Iron Overload

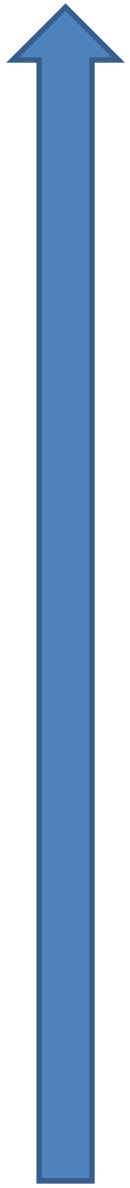
- **TRANSFERRIN SATURATION (2x)**
- (typically above 50% in women and 60% in men)

- **SERUM FERRITIN**

(abnormally high for sex, age and lifestyle habits)

DIAGNOSTIC CRITERIA: (1st Suspect!)

FERRITIN
is a highly unspecific marker of iron overload



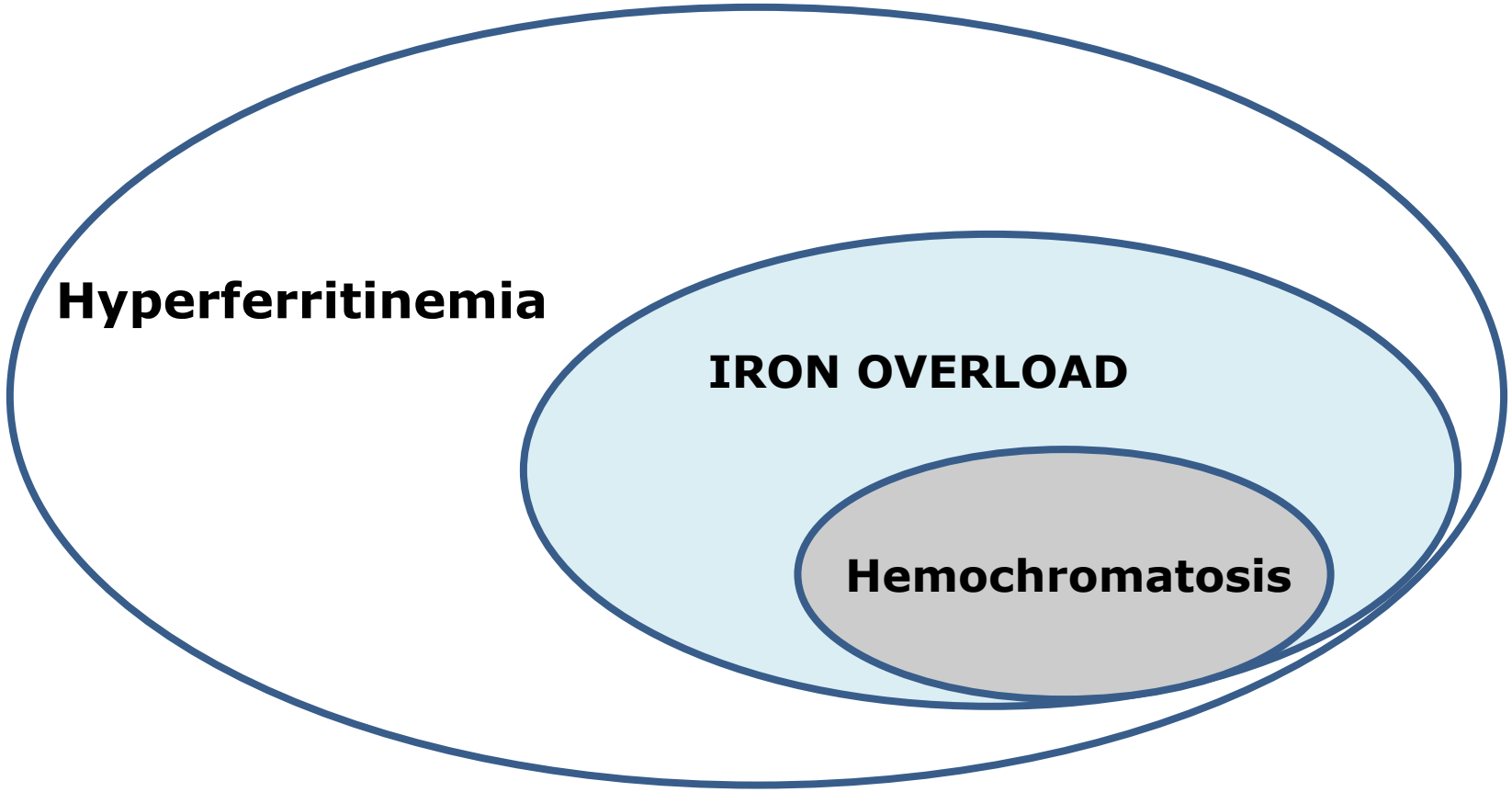
↑ release of damaged cells:
- Liver steatosis and steatohepatitis
- Chronic viral hepatitis
- Acute liver necrosis (sepsis, hepatitis, toxics)
- Auto-imunes disorders
- Acute and chronic infections
- Acute myocardial infartion
- Splenic infartion

↑ synthesis/secretion:
- Chronic Alcohol intake
- Malignancy and Chronic Inflammation
- Storage diseases (Gaucher Disease)
- Syndrome of hiperferritinemia with cataracts (mut FtL)

↑ iron overload:
- Chronic transfusion/Parentheral iron
- Iron suplementation (natives of sub-saharian Africa)
- Congenital iron loading anemias
- Aceruloplasminemia
- Hemochromatosis

Adams PC, Barton JC. A diagnostic approach to hyperferritinemia with a non-elevated transferrin saturation. J Hepatol. 2011 Aug;55(2):453-8.

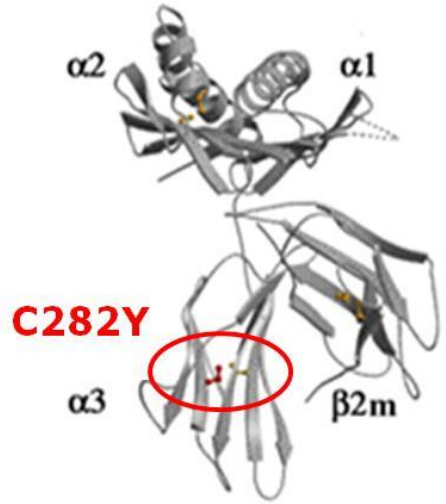
DIAGNOSTIC CRITERIA: (1st Suspect!)



The usually "confounded" terms

DIAGNOSTIC CRITERIA: (2nd Confirm!)

2nd line: Genetic Testing (HFE genotyping)



Diagnostic referral (ie, affected individual);

Result: homozygous p.C282Y.

Comment: Reports should state that, in the presence of a suggestive phenotype, this genotype supports the diagnosis of HFE-related HH. Formal diagnosis requires demonstration of increased hepatic iron stores.

European Journal of Human Genetics (2016) 24, 479–495

DIAGNOSTIC CRITERIA

Diagnostic referral (ie, affected individual);

Result: compound heterozygous p.C282Y and p.H63D.

Comment: Reports should state that, the diagnosis of the most common HFE-related HH is excluded. This genotype may predispose to mild / moderate iron overload. In patients with iron overload, other contributing factors should be considered (most commonly, alcohol consumption, fatty liver disease, and/or metabolic syndrome).

European Journal of Human Genetics (2016) 24, 479–495

Table 2 Summary of diagnostic and predictive interpretation comments for the *HFE* gene p.C282Y and p.H63D related genotypes[a]

Genotype	*Interpretation (diagnostic test)*	*Interpretation (predictive test)*
Homozygous p.C282Y NM_000410.3:c.[845G>A];[845G>A]	Compatible with the diagnosis of HFE-related HH in the presence of documented evidence of iron overload.	At risk of developing HFE-related HH. Prompt assessment of iron parameters indicated.
Compound heterozygous p.C282Y/p.H63D NM_000410.3:c.[187C>G];[845G>A]	Excludes the diagnosis of the most common form of HFE-related HH; genotype consistent with mild to moderate iron overload; Prompt the search for other causes (eg, alcohol consumption, fatty liver disease and/or metabolic syndrome).	At low risk for development of significant iron overload. May be at-risk of developing mild to modera iron overload in association with comorbid factors.
Heterozygous p.C282Y NM_000410.3:c.[845G>A];[=]	Excludes the diagnosis of the most common HFE-related HH. Other causes of iron overload should be considered.	Carrier for HFE-related HH. Is at no increased risk of developing HFE-related HH.
Homozygous p.H63D NM_000410.3:c.[187C>G];[187C>G]	Excludes the diagnosis of the most common HFE-related HH. Other causes of iron overload should be considered.	At no increased risk of developing HFE-related HH.
Heterozygous p.H63D NM_000410.3:c.[187C>G];[=]	Excludes the diagnosis of the most common HFE-related HH. Other causes of iron overload should be considered.	At no increased risk of developing HFE-related HH.
p.S65C detected NM_000410.3:c.193 A>T	In the absence of supporting evidence for a role in HH, testing for the p.S65C variant is not recommended for diagnostic purposes. If detected as an incidental finding it should not be reported but treated as 'no variant detected'.	

[a]This table summarizes key interpretation points only and should be read in conjunction with the main 'diagnostic reporting scenarios' text.

HFE-HH: a formal indication for FAMILY SCREENING

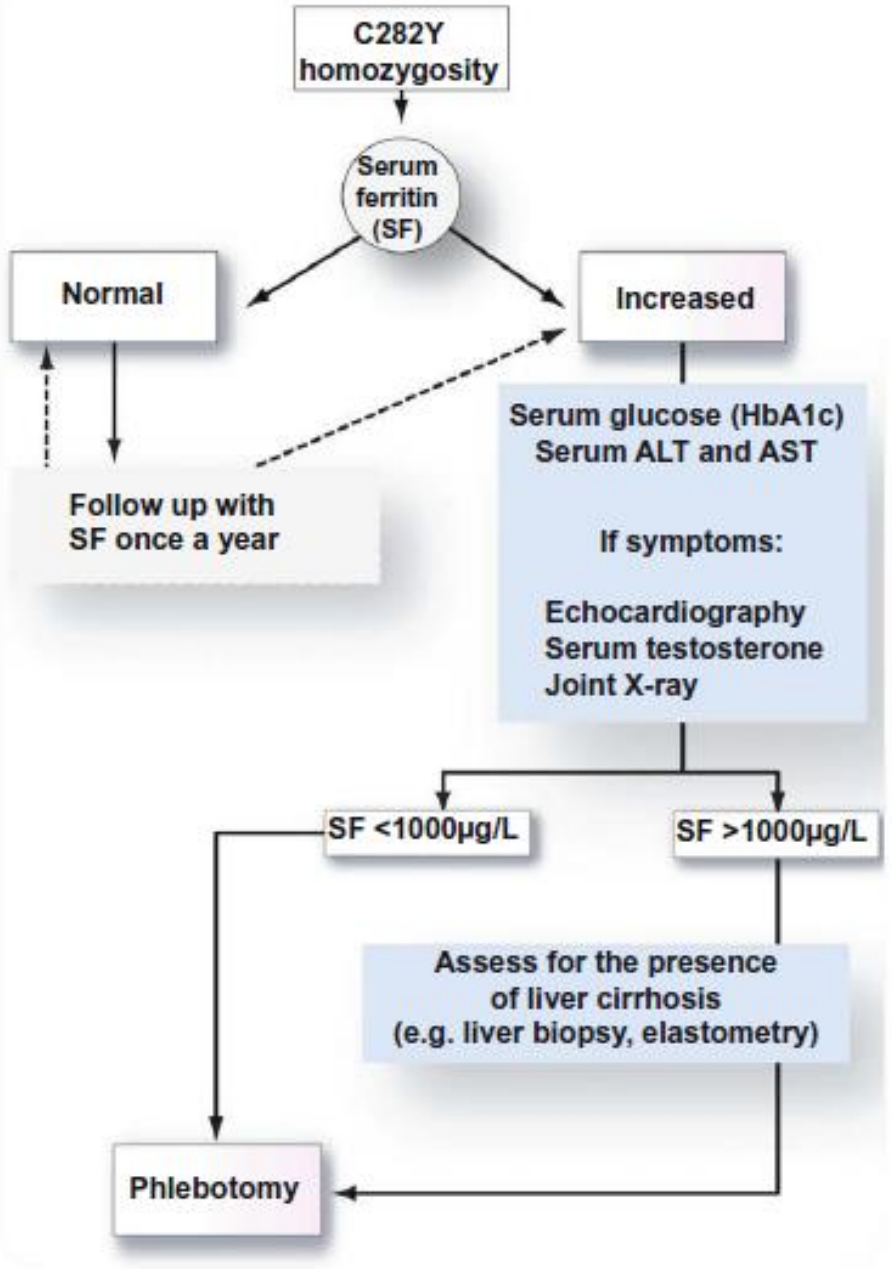
Because the prevalence of individuals at risk to develop morbidity is increased among first-degree relatives of index cases (p.C282Y homozygotes), their identification through predictive testing is appropriate.

Genetic testing of adult asymptomatic individuals should be undertaken only after appropriate counselling addressing the pros and cons of testing as well as the possible clinical consequences relating to the test result.

Eur J Hum Genet. 2016 Apr;24(4):479-95

Proposed algorithm

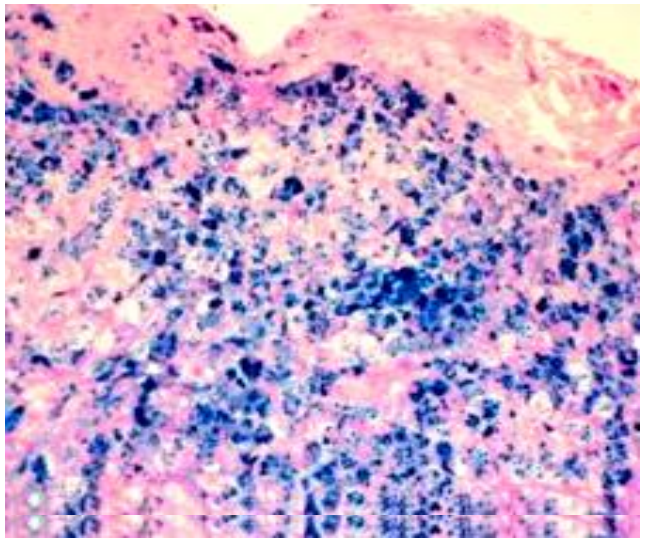
for the management of patients with C282Y homozygosity



EASL clinical practice guidelines for HFE hemochromatosis. J Hepatol. 2010 Jul;53(1):3-22.

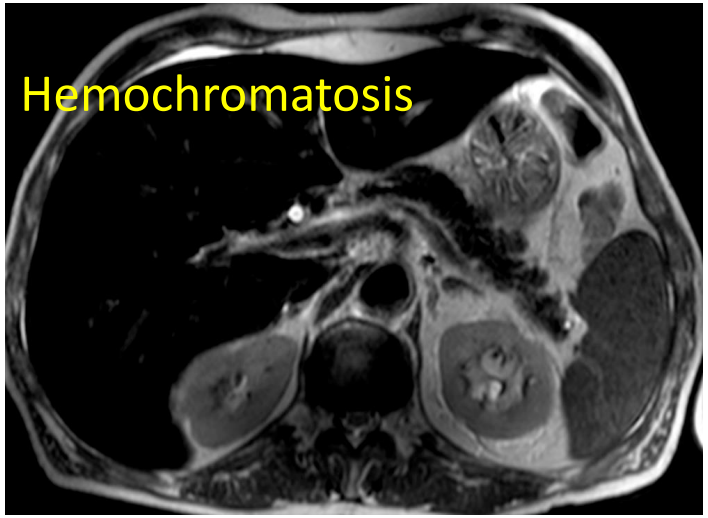
Quantifying Liver Iron Concentration (LIC)

Liver Biopsy



Iron quantification by Perls' staining

Magnetic Ressonance Imaging (MRI)



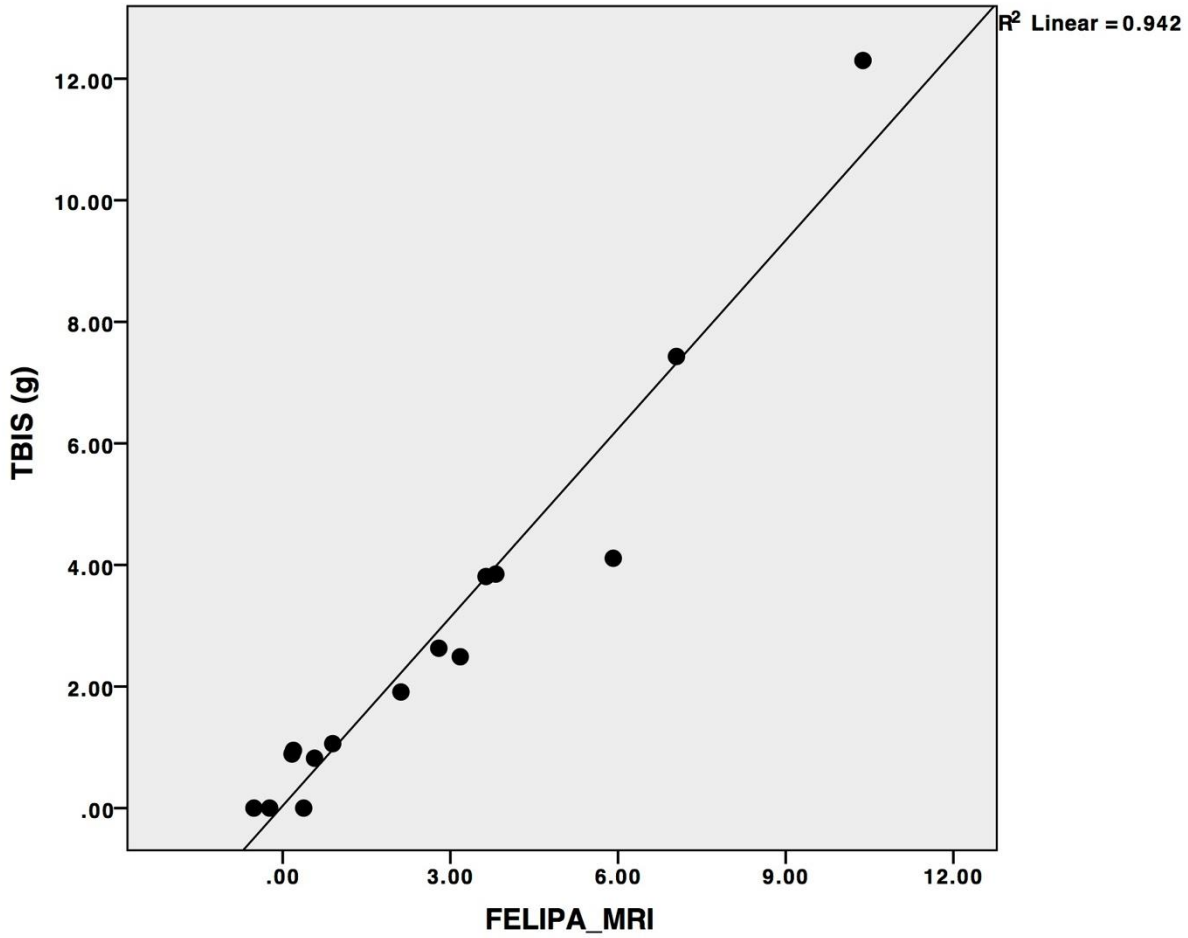
França M (personal communication)

Severe Iron Overload (>300umol/g)

Quantifying Liver Iron Concentration (R2*)

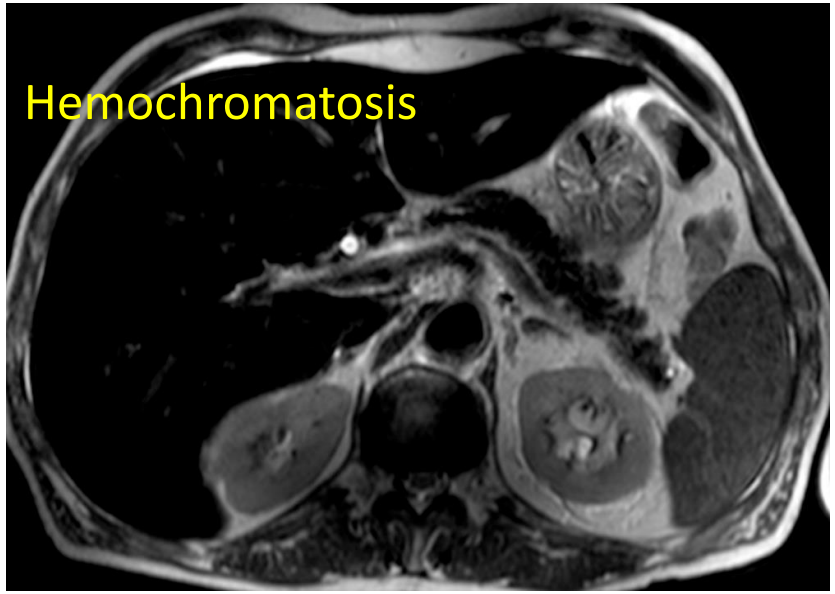
Correlation between TBIS and R2* for liver and pancreas

(FELIPA, an acronym for FErrum in LIver and PAncreas)



Quantifying Liver Iron Concentration (LIC)

Magnetic Ressonance Imaging (MRI)



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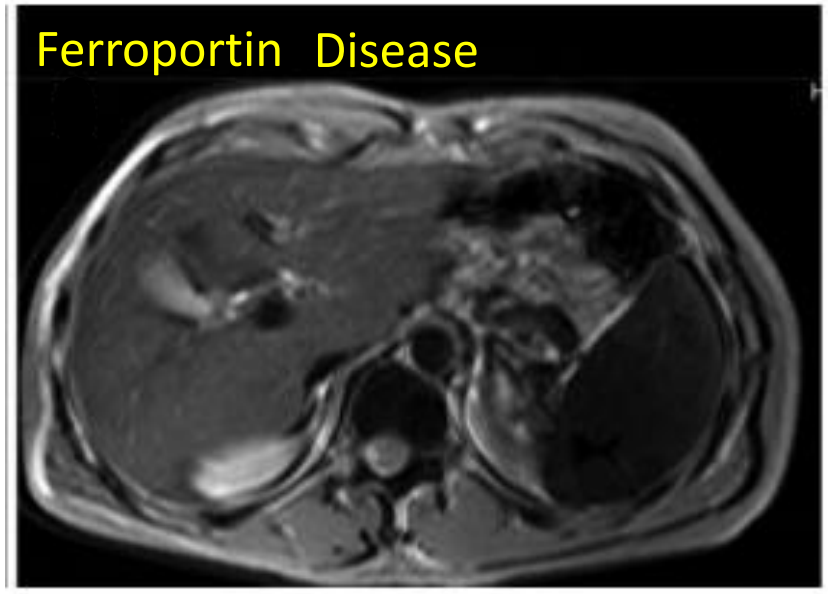
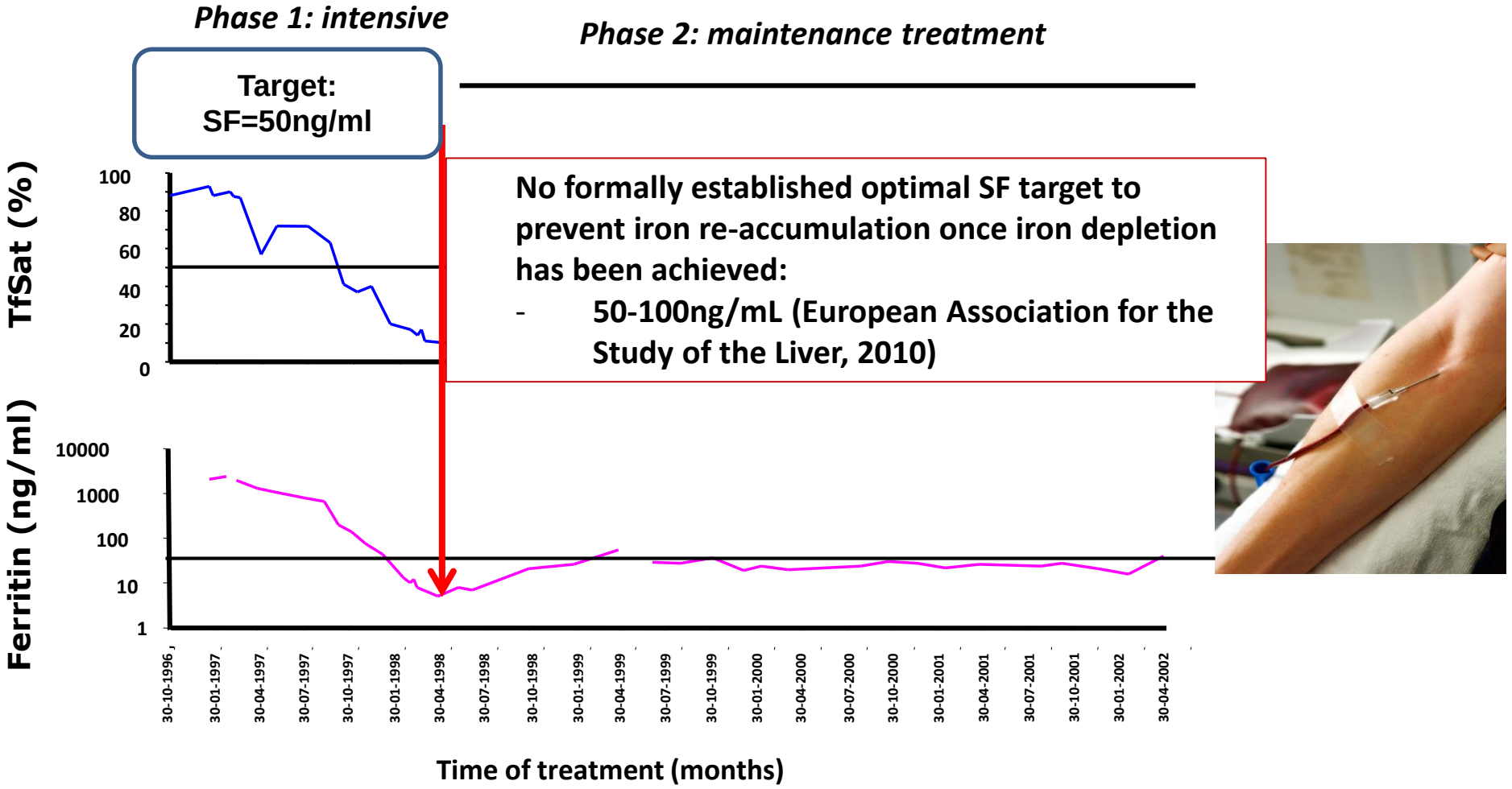


From: Antonello Pietrangelo (2014)
Clinical Liver Disease, Vol 3, No 5,
Official Learning Resource of AASLD

The standard phlebotomy treatment in HH

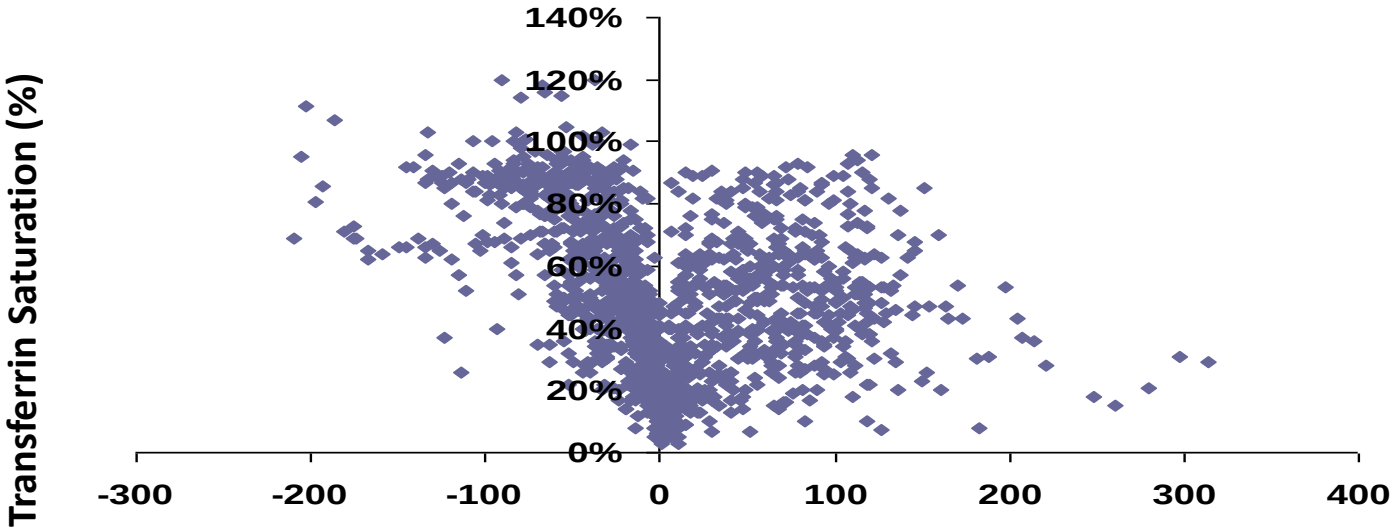


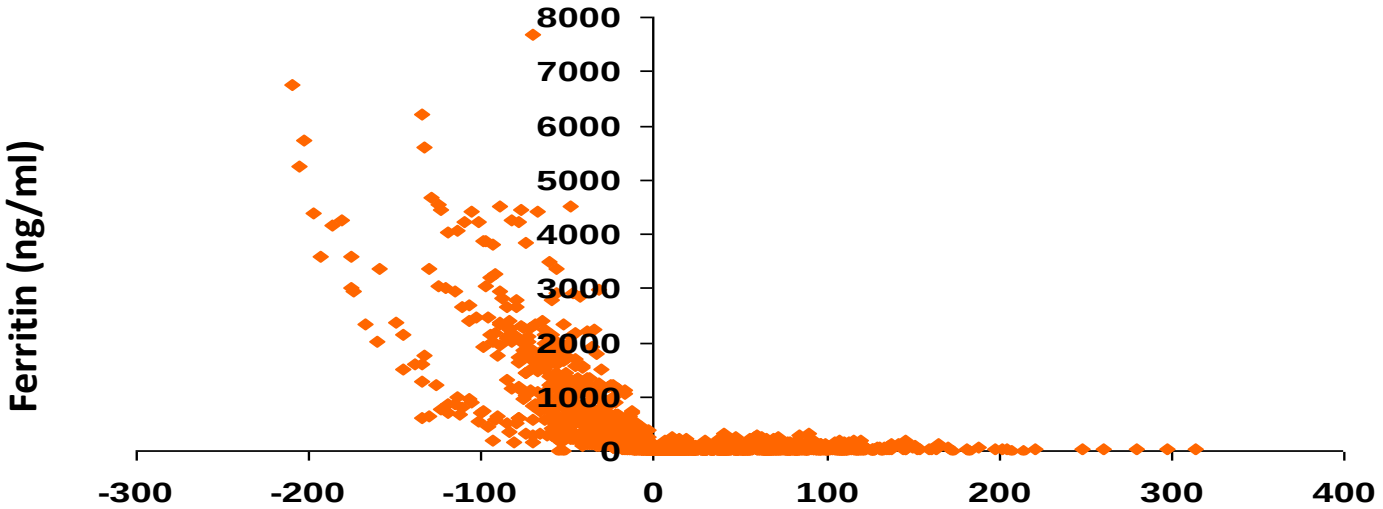
No formally established optimal SF target to prevent iron re-accumulation once iron depletion has been achieved:

- **50-100ng/mL (European Association for the Study of the Liver, 2010)**

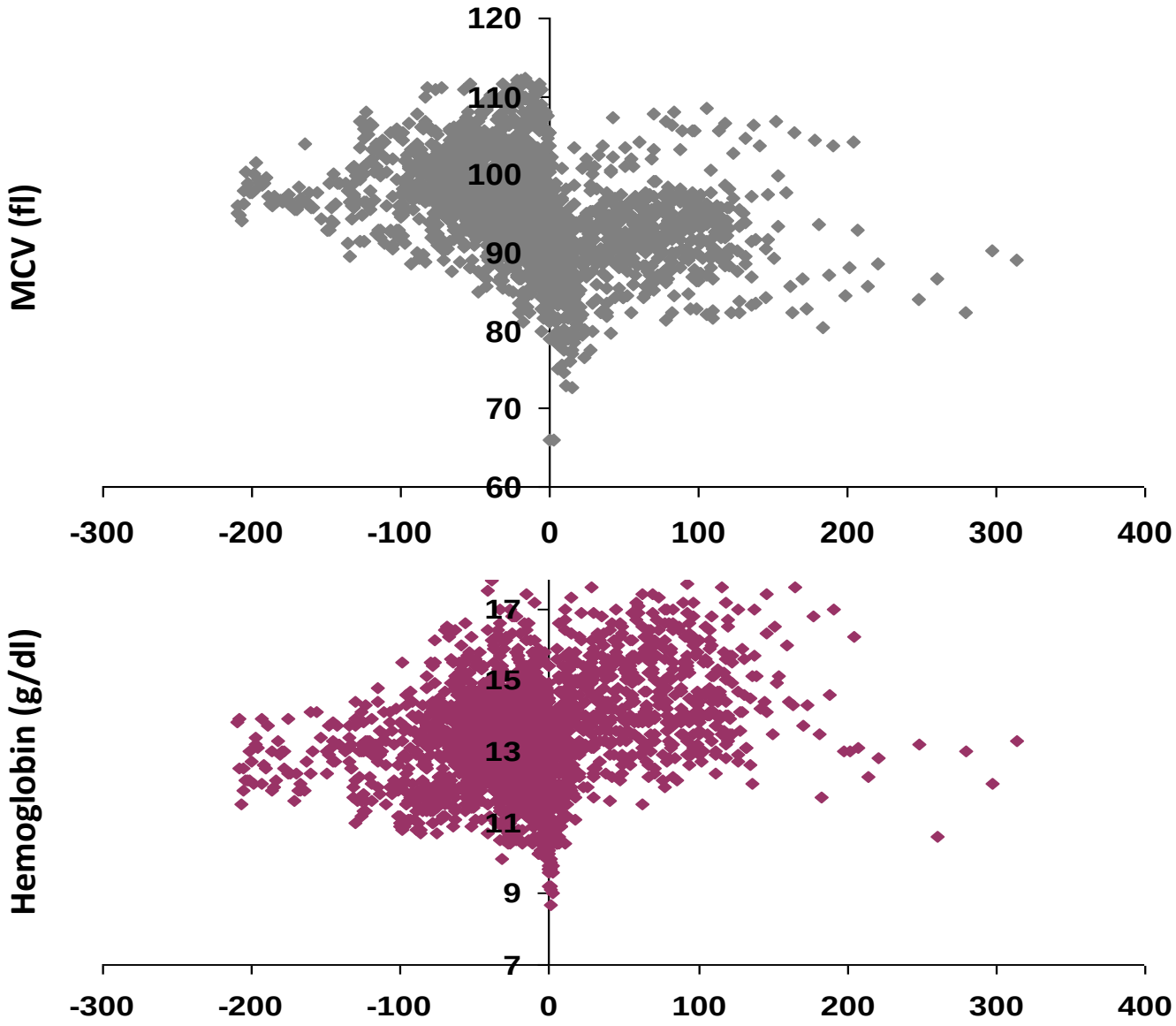
Adams et al. Hepatology International (2018) 12:83–86

Clinical follow-up during hemochromatosis treatment





Clinical follow-up during hemochromatosis treatment



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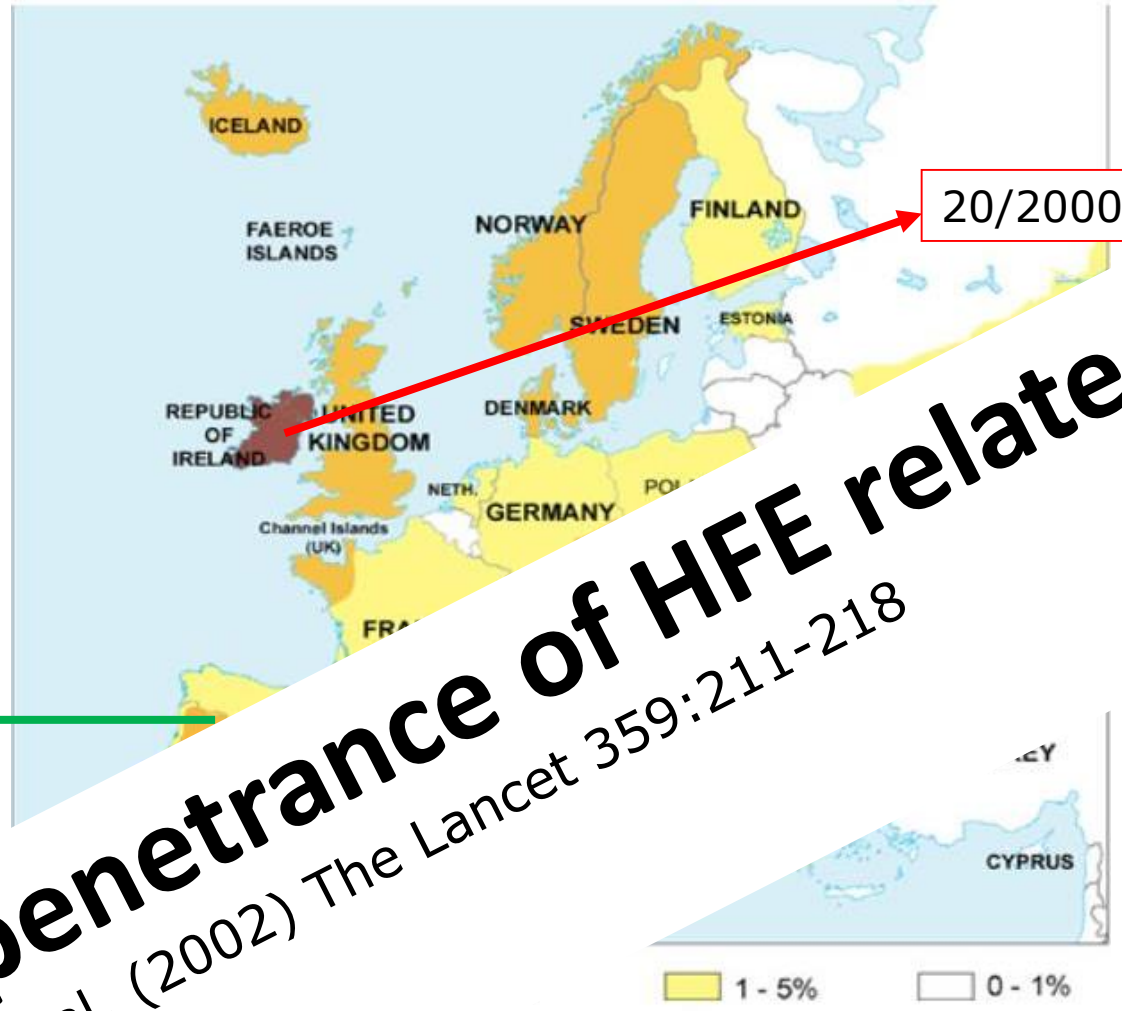
EFAPH

European Federation of Associations of Patients with Haemochromatosis

Screening: YES or NO?

Population based genetic screening for HFE-HH is not recommended



20/2000 pred

8/2000 predicted homozygotes

<1/2000 predicted homozyc

The penetrance of HFE related HH is low!

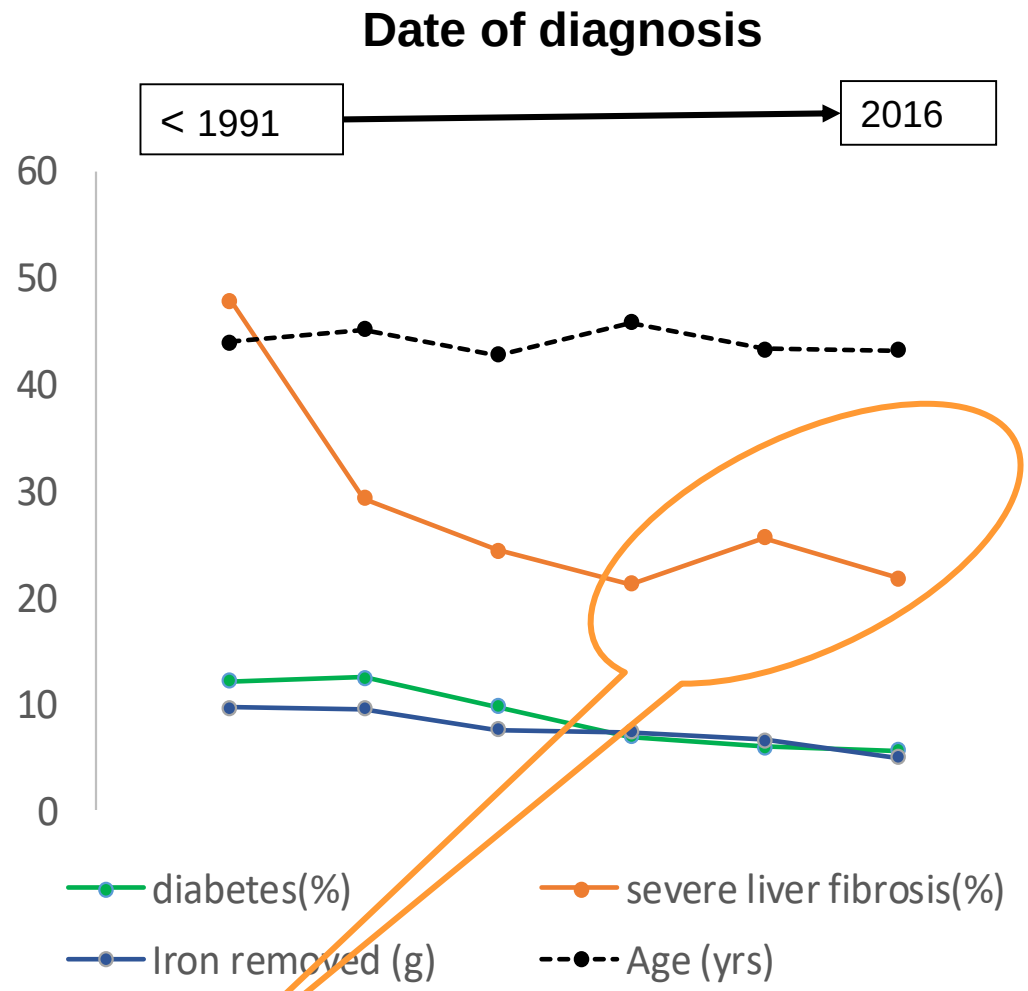
Beutler et al. (2002) The Lancet 359:211-218

of the *HFE* C282Y mutation

Enhancing early case detection?

Reduced phenotypic expression in genetic hemochromatosis with time

Deugnier et al, J Hepatol. 2019 Jan;70(1):118-125.



Can we further decrease these 20% frequency of C282Y homozygous males with severe liver fibrosis?

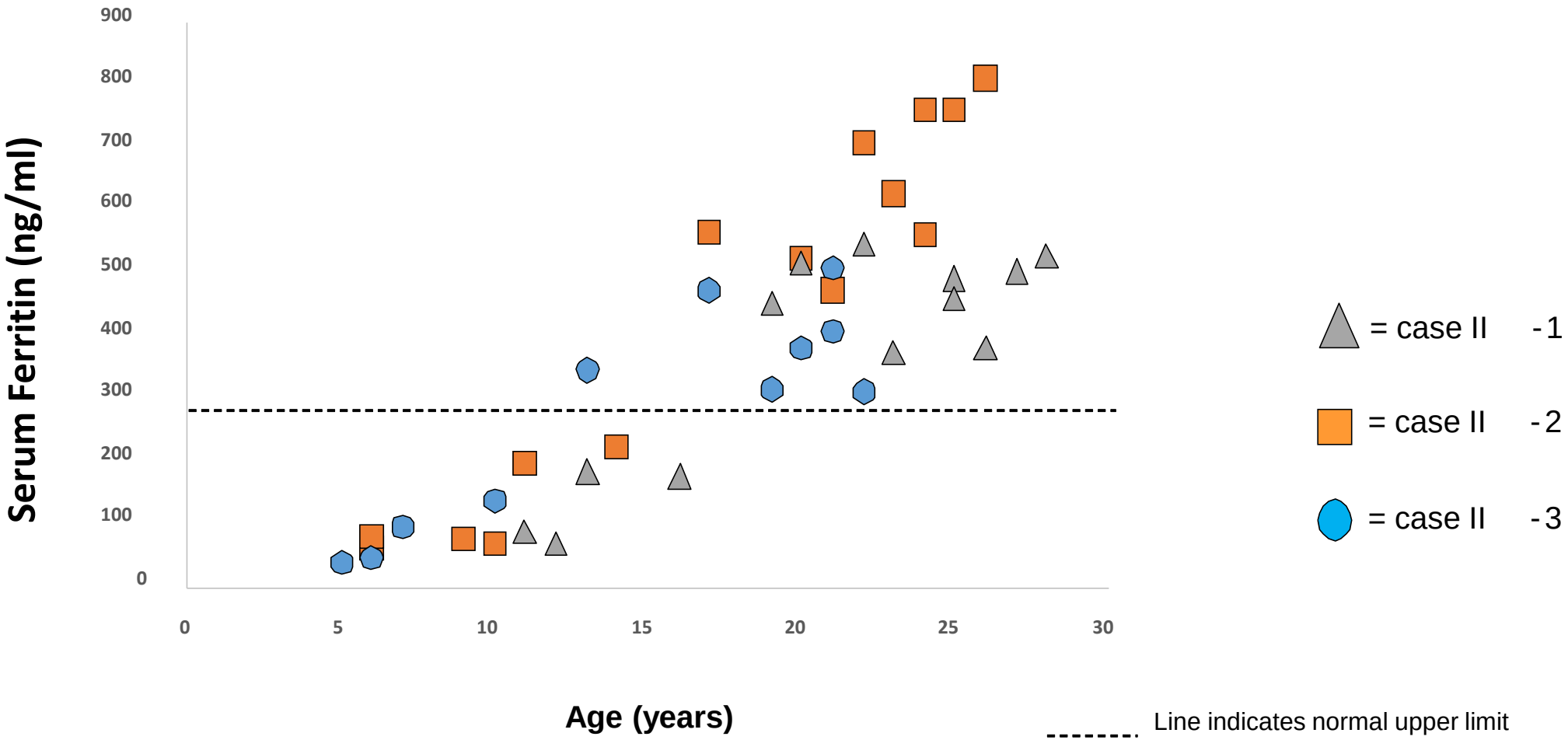
Enhancing early case detection?

*Powell et al. Arch Intern Med. (*2006)

"*Our estimate of the rate of iron accumulation with age indicates that the mean age of homozygotes with severe hepatic iron overload would be approximately* ***21 years after the hepatic iron stores begin to increase*** *in both men and woman*."

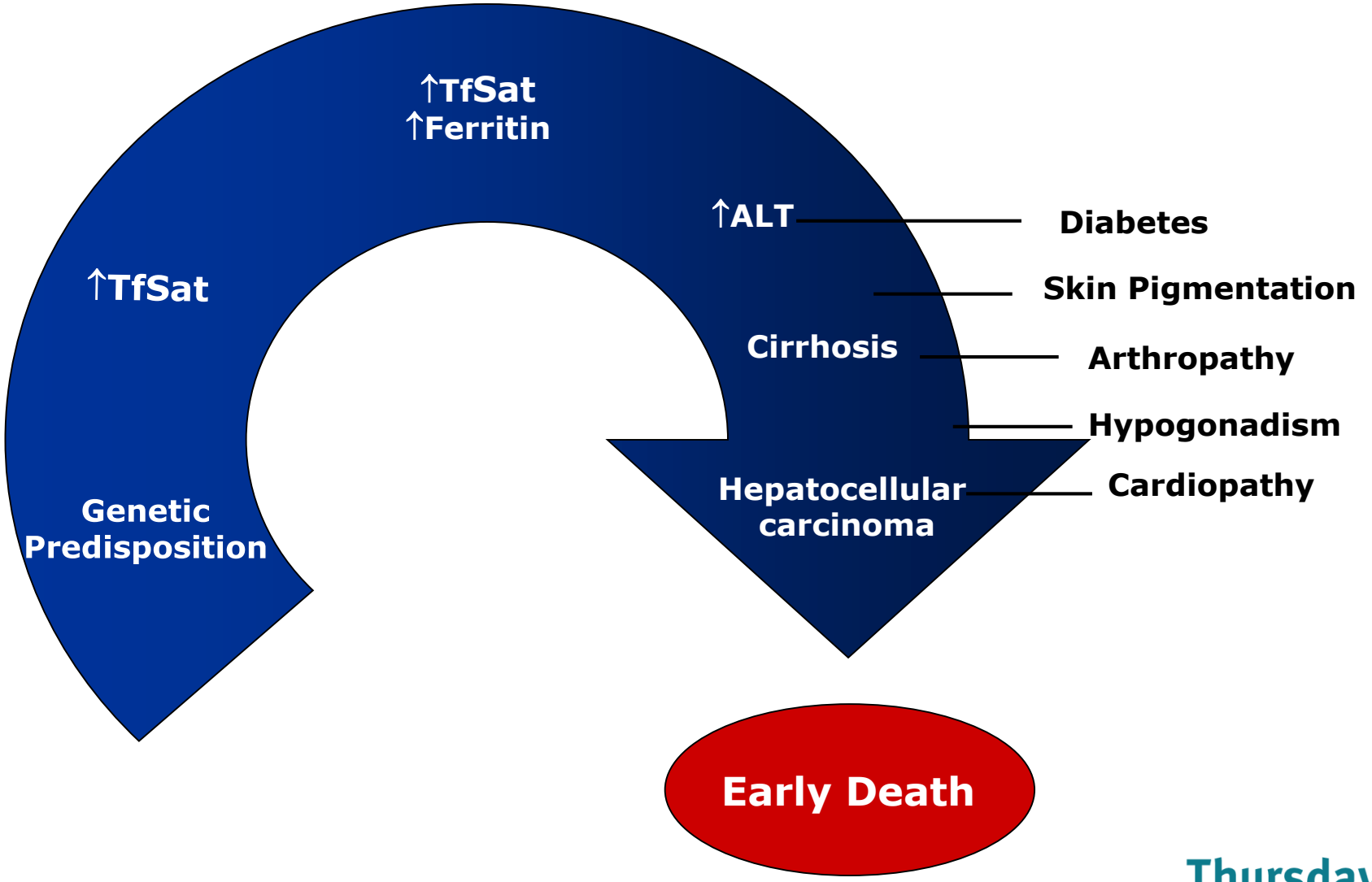
The largest longitudinal study with a 24yrs follow-up of 672 HH cases with ages ranging from 10-73 in males and from 6-89 in females.

Enhancing early case detection?



Take home messages

The clinical spectrum of Hemochromatosis



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Take home messages

- **The best strategies to prevent the severe clinical consequences of HFE-related hemochromatosis are:**
  - To increase awareness, particularly among general practitioners, in order to enhance early case detection, perform a correct diagnosis and implement family screening in adult first degree relatives

- We advocate the early population biochemical screening (18-20 years) with confirmatory genetic testing to prevent severe liver disease