Thursdays Webinars

EuroBloodNet

Challenges in the Management of HFE-related Hemochromatosis

Graça Porto
Coordinator of the subnetwork*: Hemochromatosis and other disorders of iron metabolism and heme synthesis*
Centro Hospitalar Universitário de Santo António (CHUdSA)
Centro de Genética Preditiva e Preventiva (CGPP/IBMC)
Porto– Portugal
11th April 2024

Co-funded by
the Health Programme
of the European Union

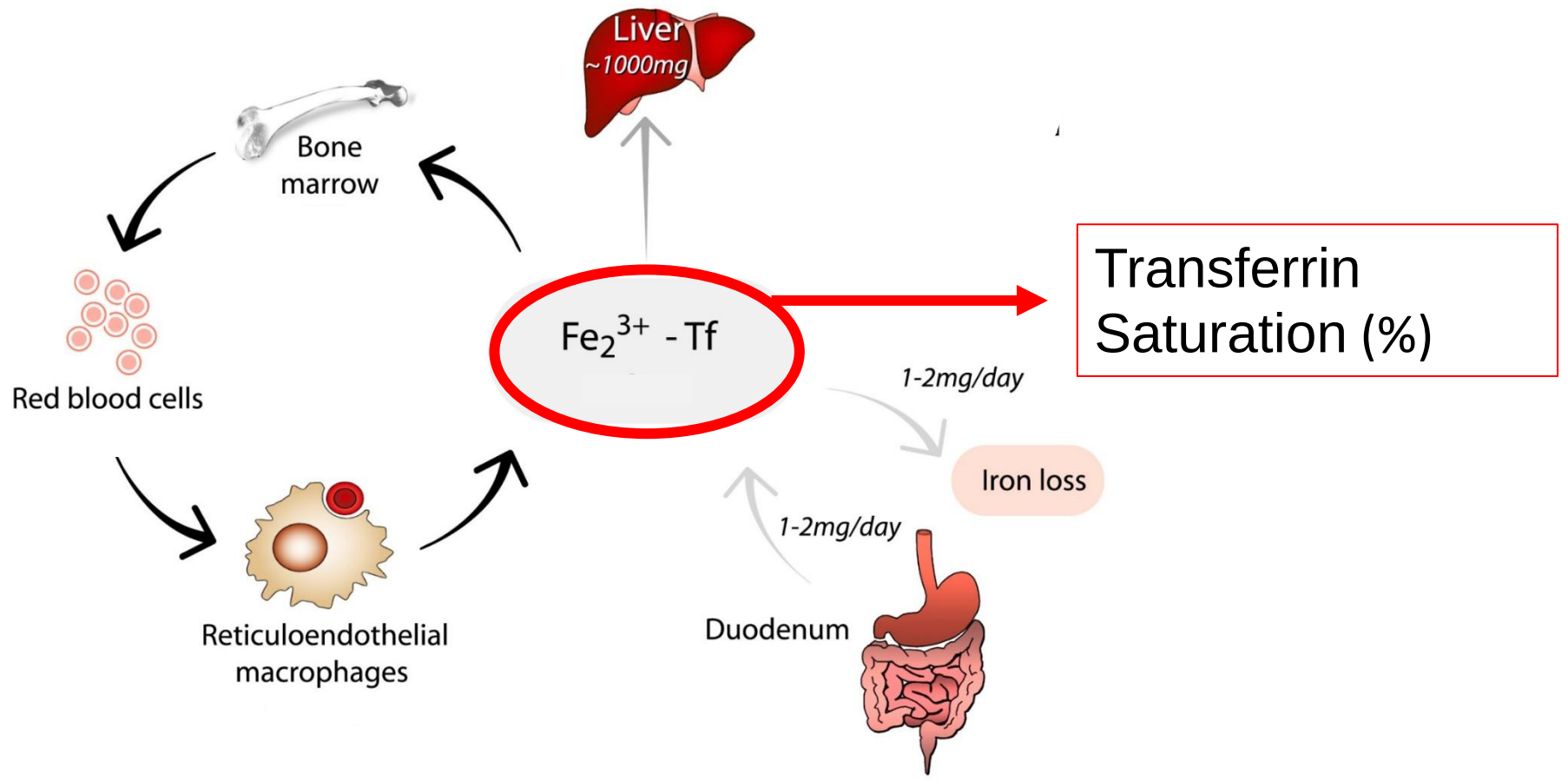
European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Nothing to Declare

Learning objectives of the webinar

1. INTRODUCING THE PHYSIOPATHOLOGY OF HEMOCHROMATOSIS
2. UPDATE ON NOMENCLATURE AND CLASSIFICATION
3. THE MAIN CHALLENGES IN THE MANGEMENT OF HFE- related HEMOCHROMATOSIS

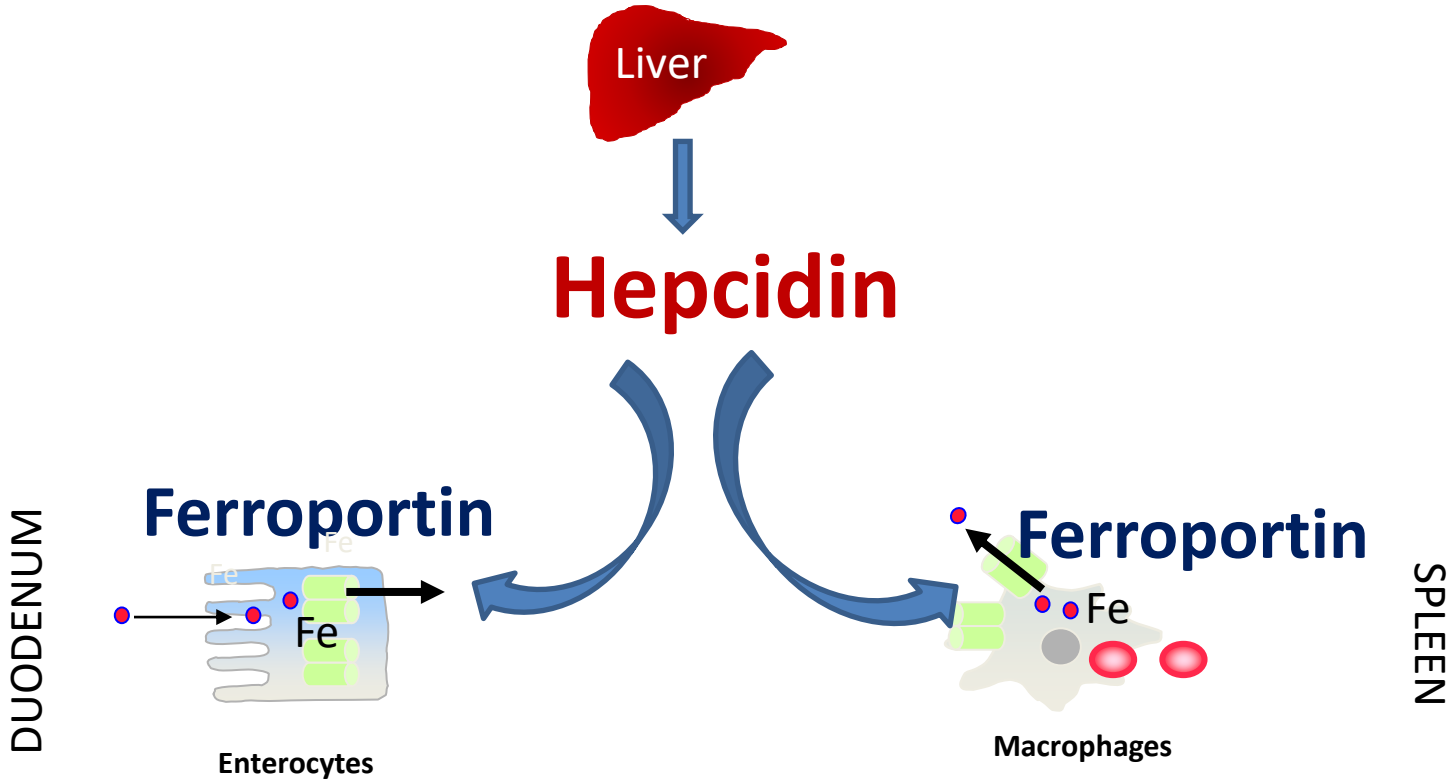
REGULATION OF IRON HOMEOSTASIS



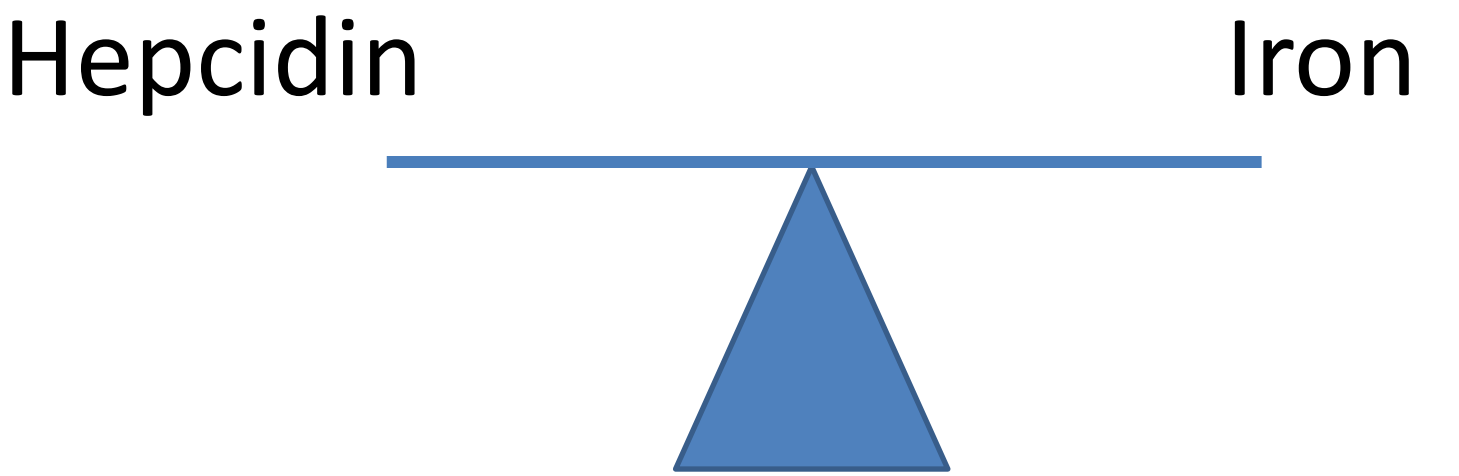
Adapted from: *Hentze, Muckenthaler and Andrews, Cell (2004)*

REGULATION OF IRON HOMEOSTASIS

The hepcidin-ferroportin axis regulates iron transport to the blood

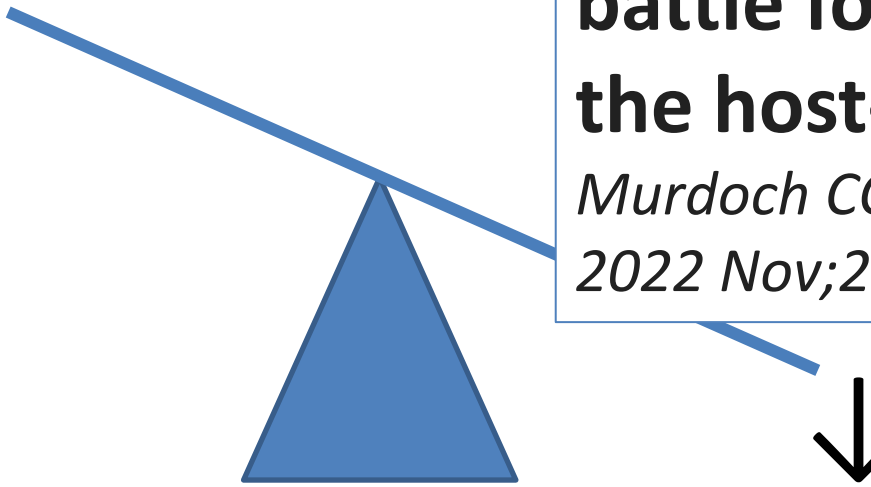


Hepcidin: maintains the iron equilibrium in the body



Hepcidin up-regulation decreases serum iron levels

↑Hepcidin

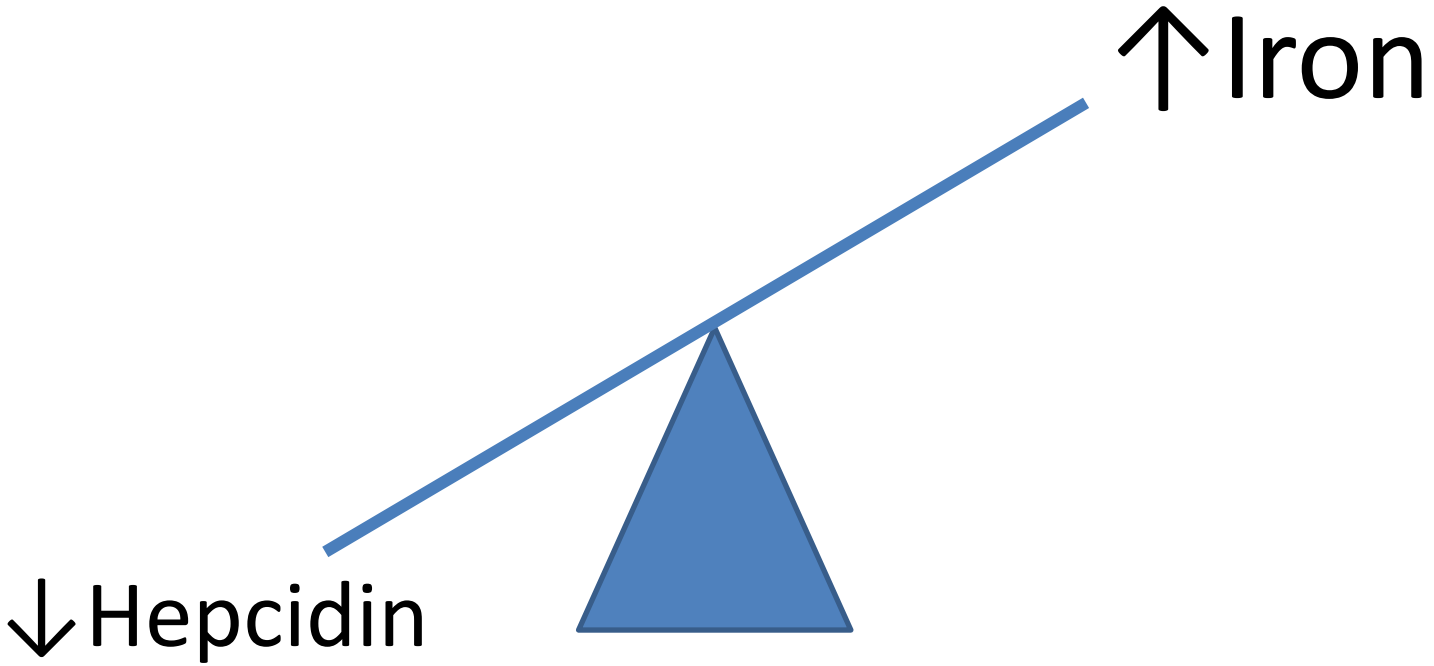


↓Iron

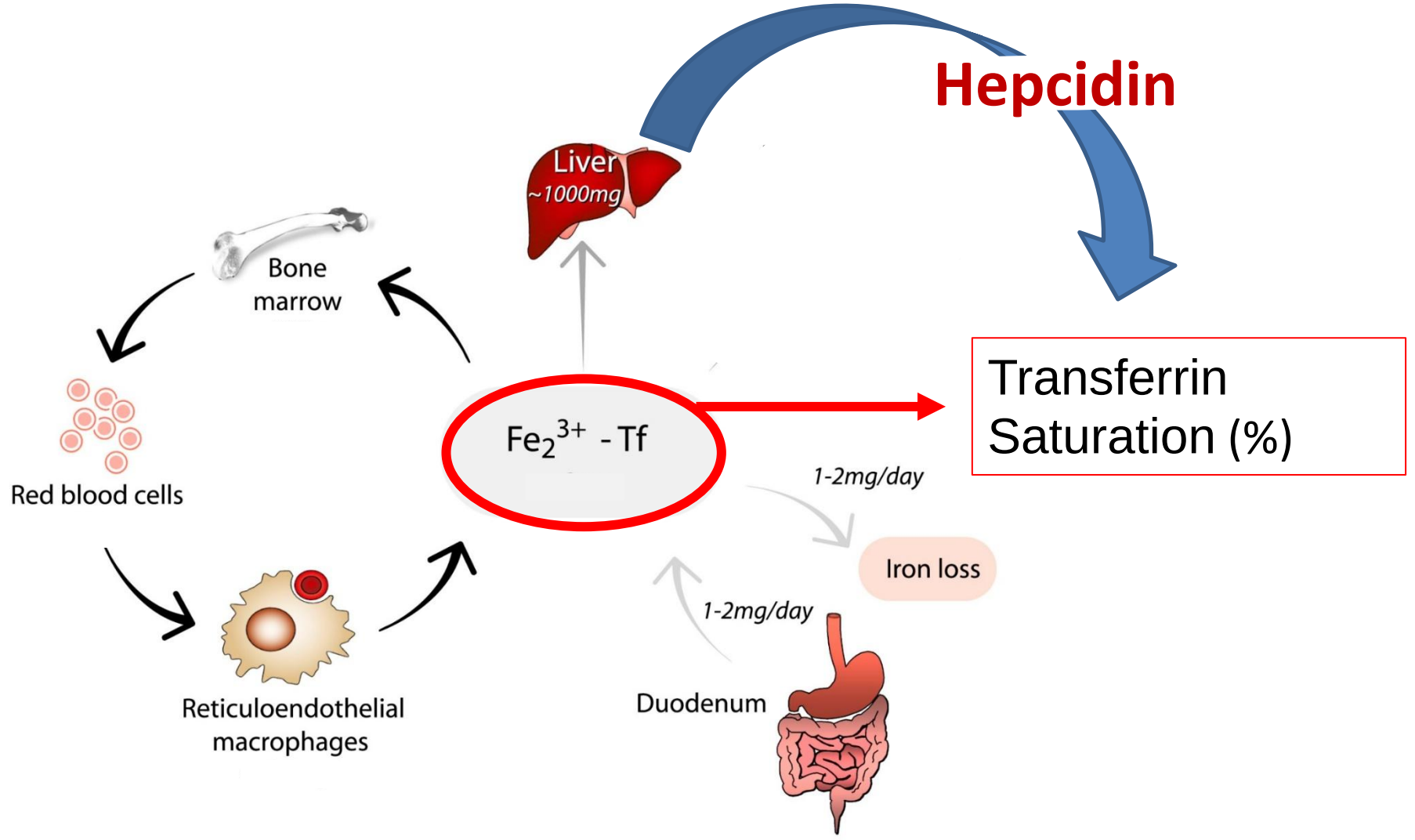
Nutritional immunity: the battle for nutrient metals at the host-pathogen interface.

Murdoch CC, Skaar EP. Nat Rev Microbiol. 2022 Nov;20(11):657-670.

Hepcidin down-regulation increases serum iron levels



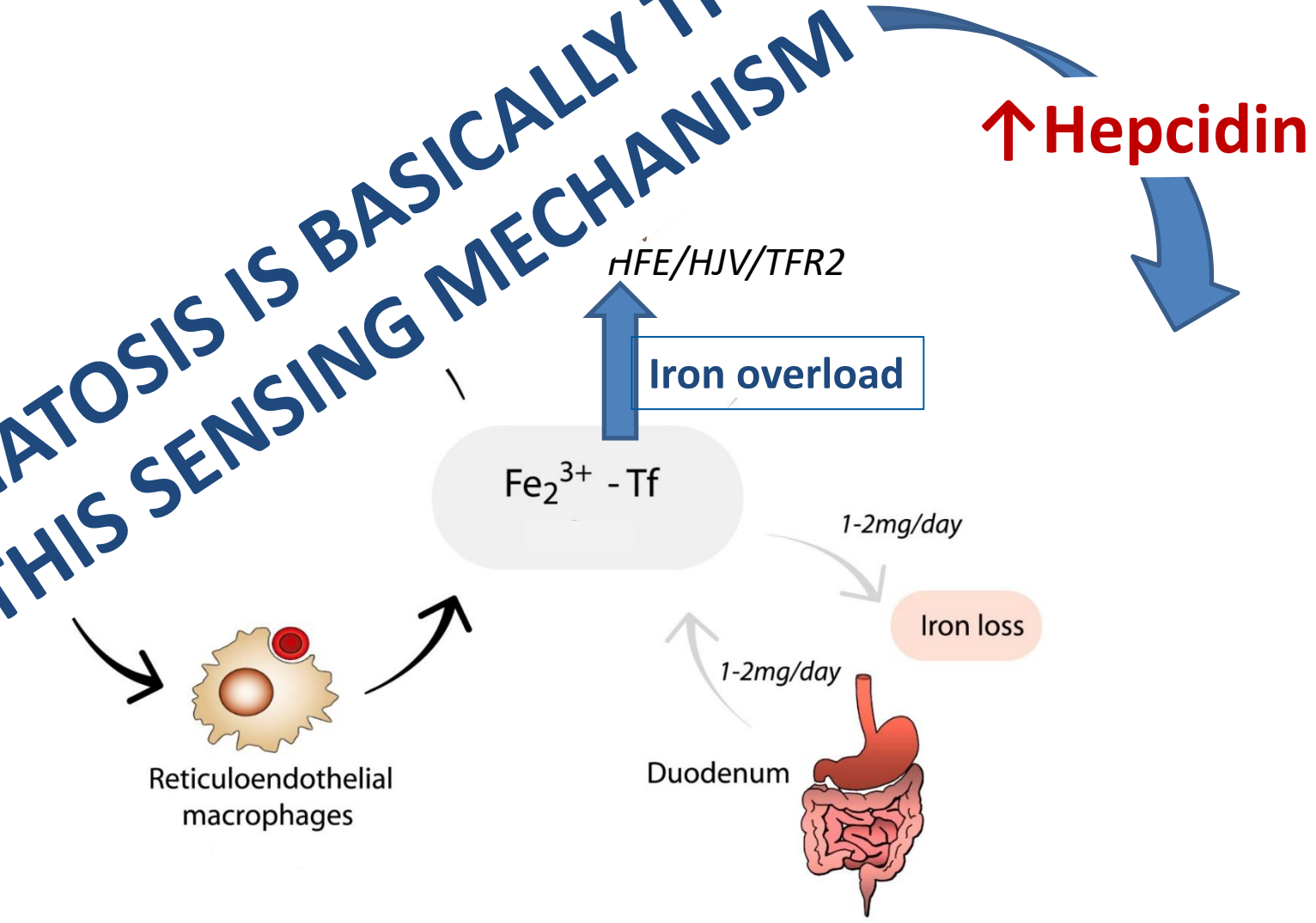
REGULATION OF IRON HOMEOSTASIS



Adapted from: *Hentze, Muckenthaler and Andrews, Cell (2004)*

THE LIVER IS THE "SENSOR" OF IRON NEEDS

HEMOCHROMATOSIS IS BASICALLY THE FAILURE OF THIS SENSING MECHANISM

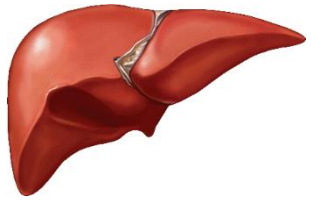


Adapted from: *Hentze, Muckenthaler and Andrews, Cell (2004)*

SUMMARY OF THE PATHOPHYSIOLOGY OF HEMOCHROMATOSIS

GENETIC TESTING

GENETIC DEFECT (*hemochromatosis proteins*)



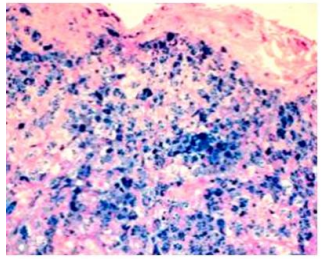
↓Hepcidin

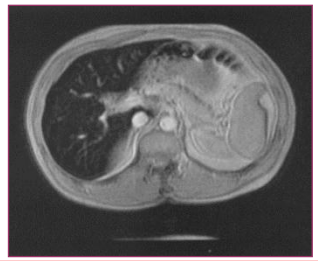
↑ ↑ **Serum Transferrin saturation**

Tissue iron overload

PANCREAS
HYPOPHYSIS
HEART

LIVER

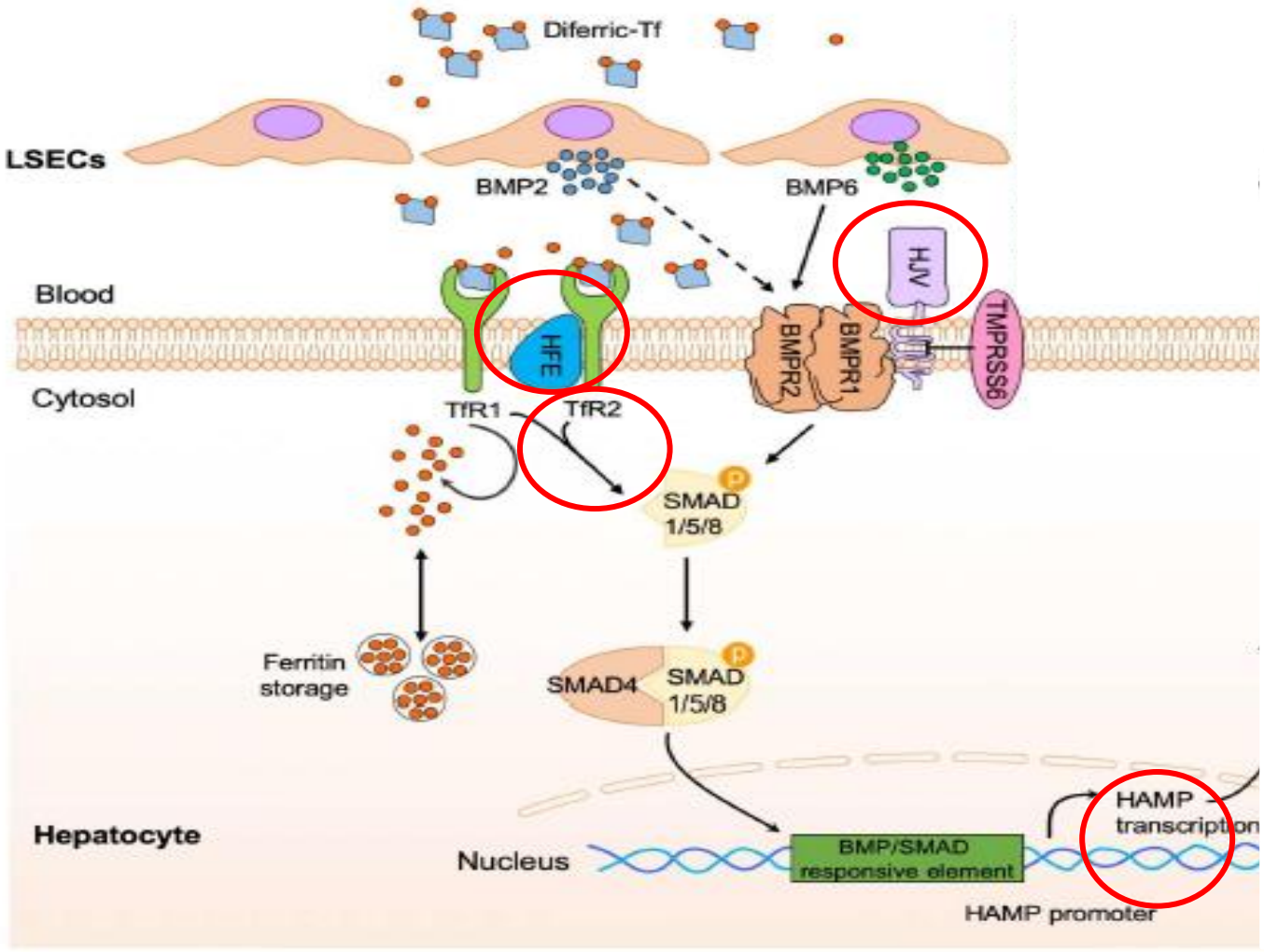




↑ ↑ **Serum Ferritin**

ARTHROPATHY?

HEMOCHROMATOSIS CLASSIFICATION *(Girelli et al. Blood. 2022 May 19;139(20):3018-3029)*



HFE-related

>90%

p.C282Y/p.C282Y

p.C282Y/rare *HFE* mutations

Non-HFE-related:

Transferrin receptor 2 (*TFR2*)
Hemojuvelin (*HJV*)
Hepcidin (*HAMP*)

rare

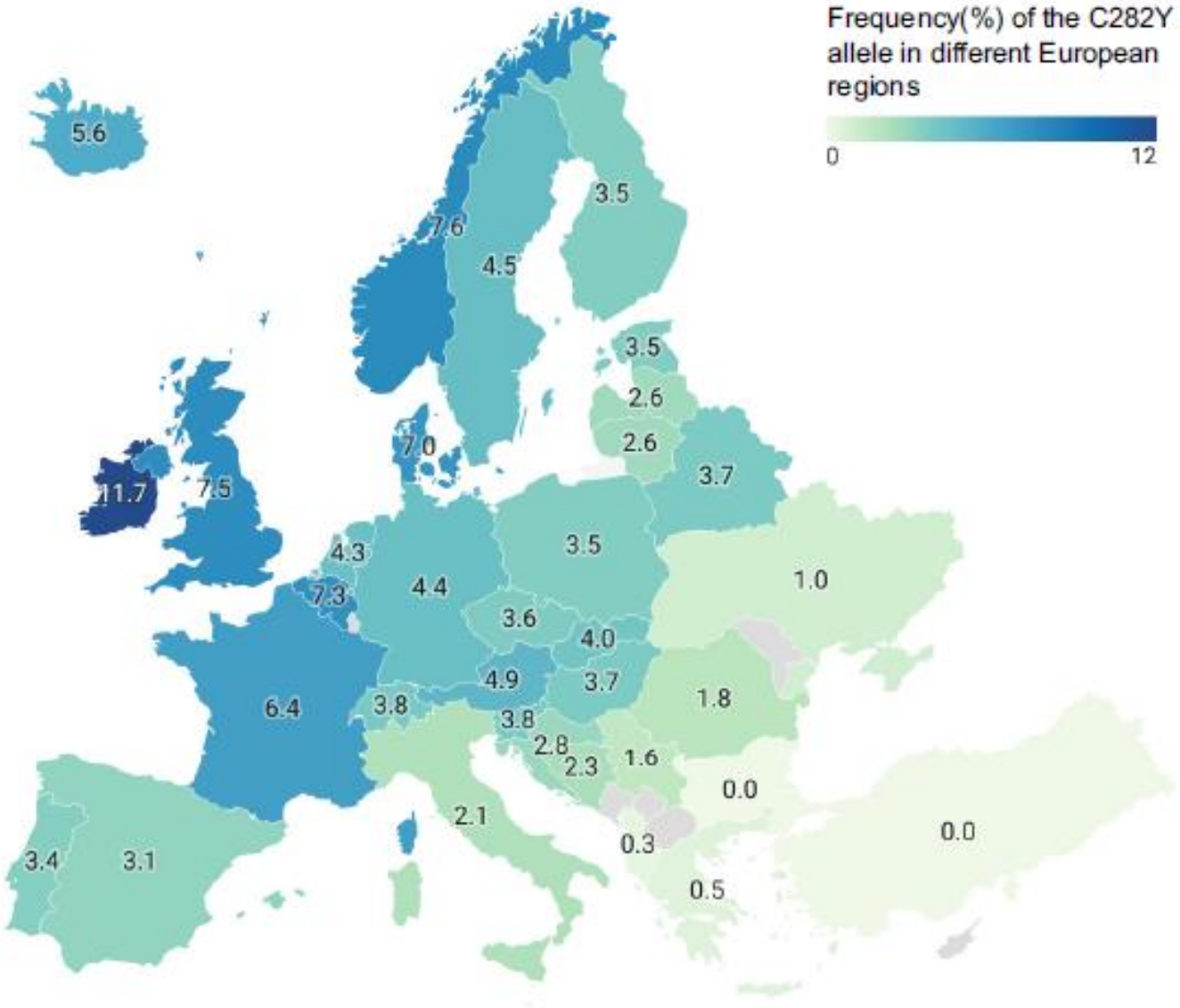
Ferroportin (*FPN*)
Digenic

Extremely rare

HFE-related hemochromatosis
p.C282Y/p.C282Y

↑ Frequency of people at risk in northern european countries

↓ Penetrance of severe clinical manifestations of the disease



From: EASL Clinical Practice Guidelines on haemochromatosis. J Hepatol. 2022 May 30:S0168-8278(22)00211-2.

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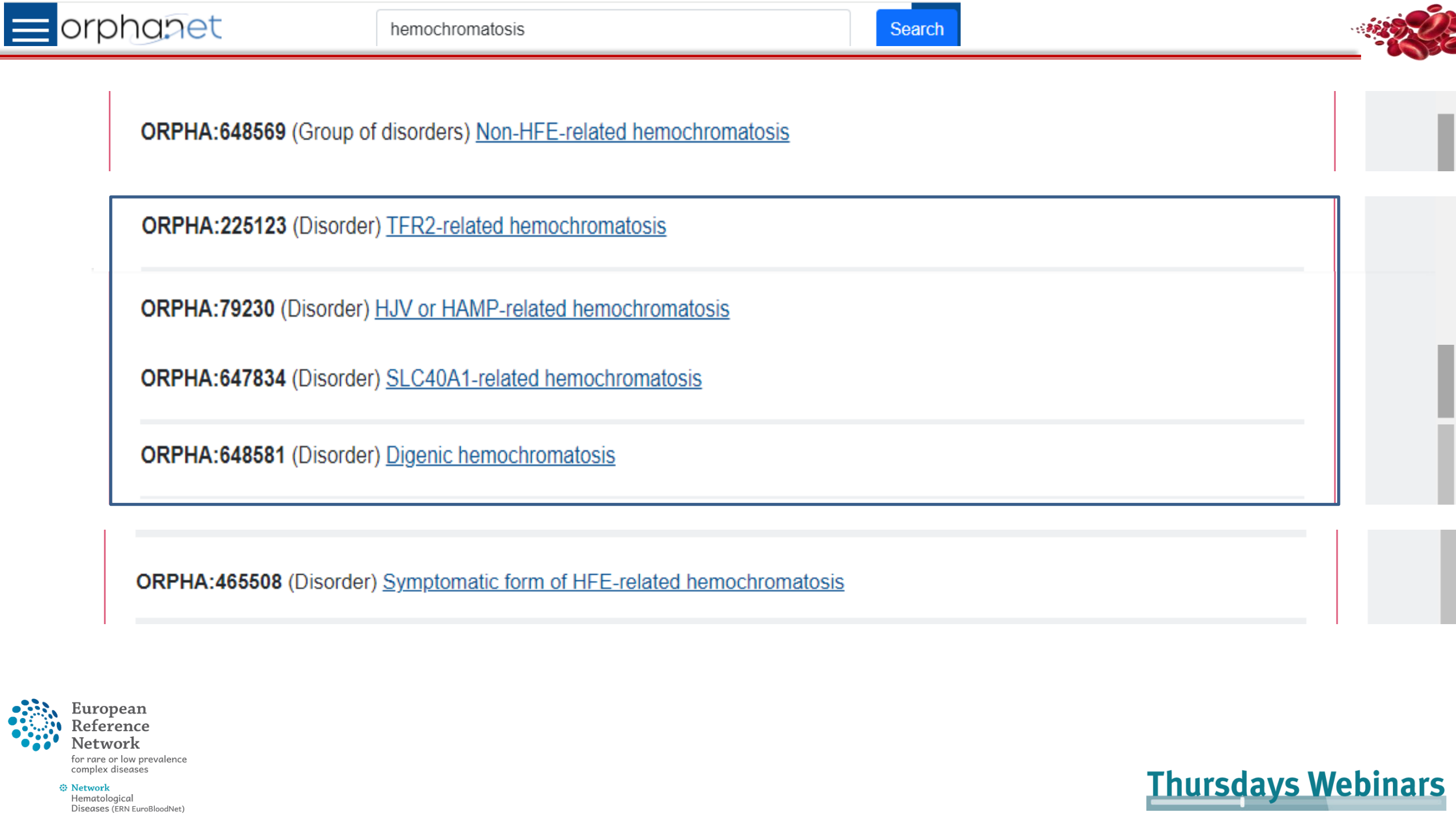
orphanet
hemochromatosis
Search
ORPHA:648569 (Group of disorders) Non-HFE-related hemochromatosis
ORPHA:225123 (Disorder) TFR2-related hemochromatosis
ORPHA:79230 (Disorder) HJV or HAMP-related hemochromatosis
ORPHA:647834 (Disorder) SLC40A1-related hemochromatosis
ORPHA:648581 (Disorder) Digenic hemochromatosis
ORPHA:465508 (Disorder) Symptomatic form of HFE-related hemochromatosis

THE MAIN CHALLENGES IN THE MANAGEMENT OF HEMOCHROMATOSIS

(*how to detect, diagnose and treat earlier?)*

- ENHANCE CASE DETECTION
- THE QUESTION OF POPULATION SCREENING
- IDENTIFY MODIFIERS OF CLINICAL PENETRANCE
- TREATMENT OPTIONS

ENHANCE CASE DETECTION

Adults presenting with any of the following should be screened for haemochromatosis:

- Fatigue, arthralgias
- Family history of haemochromatosis
- Chronic liver disease, primary liver cancer
- Arthritis, osteoporosis
- Diabetes

↓

Iron panel:

- Transferrin saturation (TSAT)
  (serum iron + transferrin or TIBC)
- Serum ferritin

→ **Unexplained** persistently elevated

↑ *HFE* genotyping for p.C282Y

EASL Clinical Practice Guidelines on haemochromatosis. J Hepatol. 2022 Aug;77(2):479-502.

Published in final edited form as:
Hepatology. 2012 June ; 55(6): 1722–1726. doi:10.1002/hep.25538.

Probability of C282Y homozygosity decreases as liver transaminase activities increase in participants with hyperferritinemia in the HEIRS Study

Paul C. Adams[1], Mark Speechley[2], James C. Barton[3], Christine E. McLaren[4], Gordon D. McLaren[5], and John H. Eckfeldt[6]

ENHANCE CASE DETECTION

Adults presenting with any of the following should be screened for haemochromatosis:

- Fatigue, arthralgias
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- Chronic liver disease, primary liver cancer
- Arthritis, osteoporosis
- Diabetes

Iron panel:

- Transferrin saturation (TSAT)
  (serum iron + transferrin or TIBC)
- Serum ferritin
- Full blood count + reticulocytes
  (to exclude anaemia and red cell disorders)

Unexplained persistently elevated → *HFE* genotyping for p.C282Y

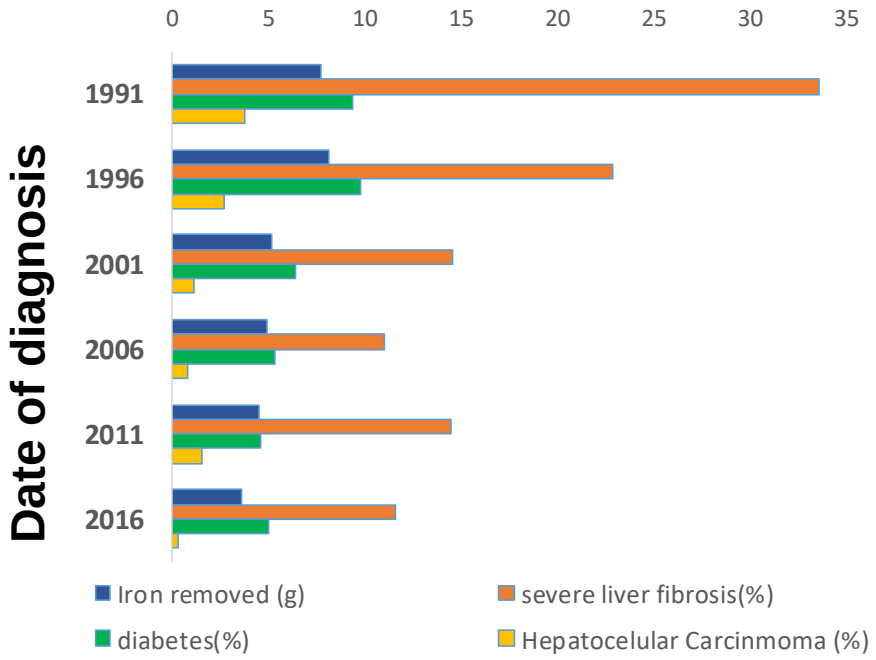
EASL Clinical Practice Guidelines on haemochromatosis. J Hepatol. 2022 Aug;77(2):479-502.

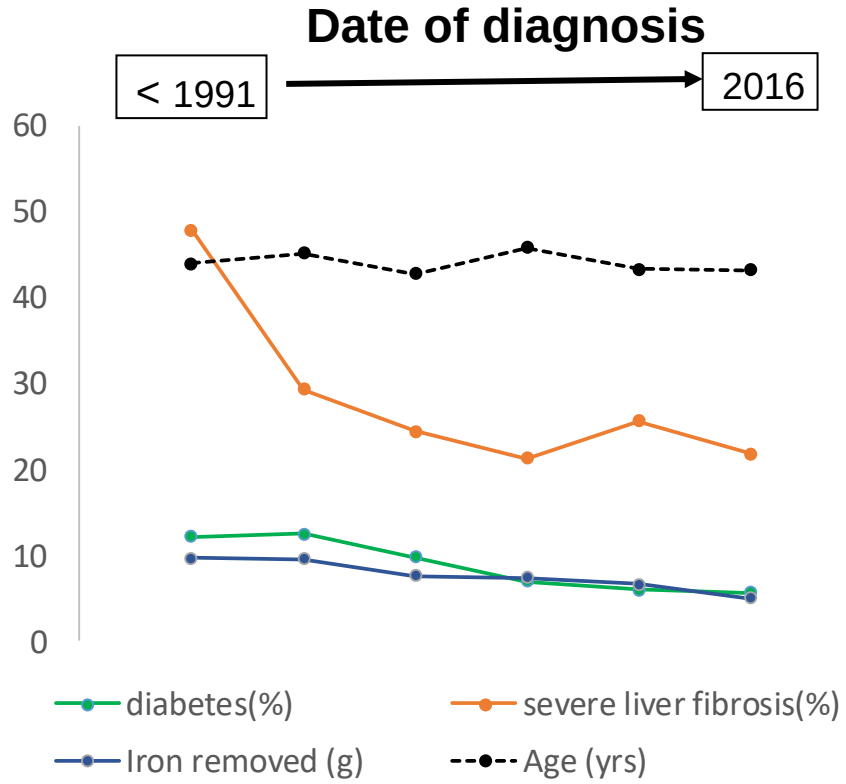
ENHANCE CASE DETECTION

Inform and recommend family screening in all adult first degree family members of patients homozygous for the C282Y variant.

EASL Clinical Practice Guidelines on haemochromatosis. J Hepatol. 2022 Aug;77(2):479-502.

Reduced phenotypic expression in genetic hemochromatosis with time: role of exposure to non-genetic factors





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

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Haemochromatosis International

EFAPH Fe

Consensus on population screening for HFE-Hemochromatosis: a Delphi study

1. Should population screening for hemochromatosis be recommended?

2. Which tests should be used?

3. At what age should population screening and follow-up occur?

(Consensus defined as ≥75% agreement on each of these key questions)

We achieved consensus for screening for *HFE*-related hemochromatosis in high prevalence populations (>0.4%) before the age of 30 years

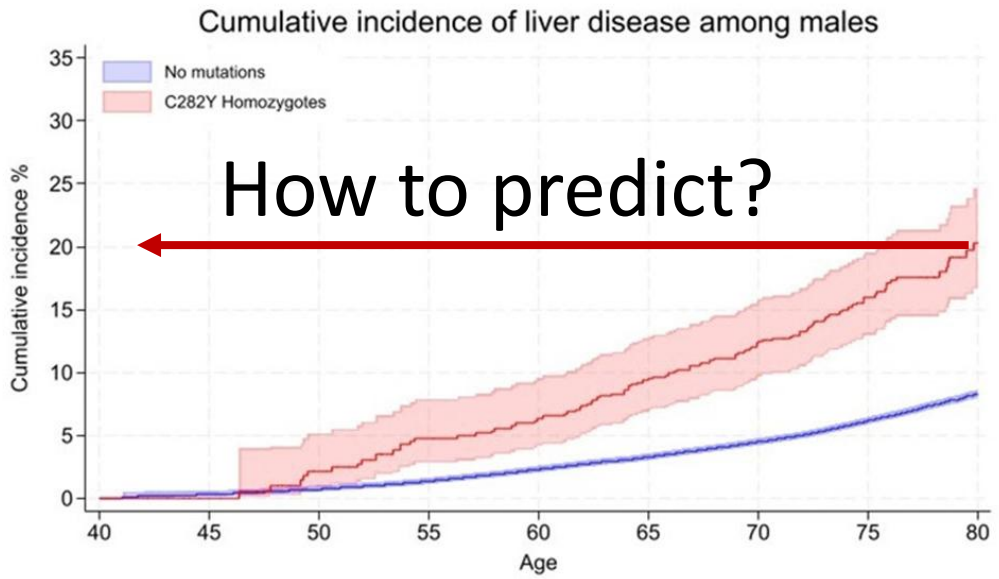
BUT **NO CONSENSUS ON METHOD**

BIOCHEMICAL (TRANSFERRIN SATURATION)? – UNSPECIFIC

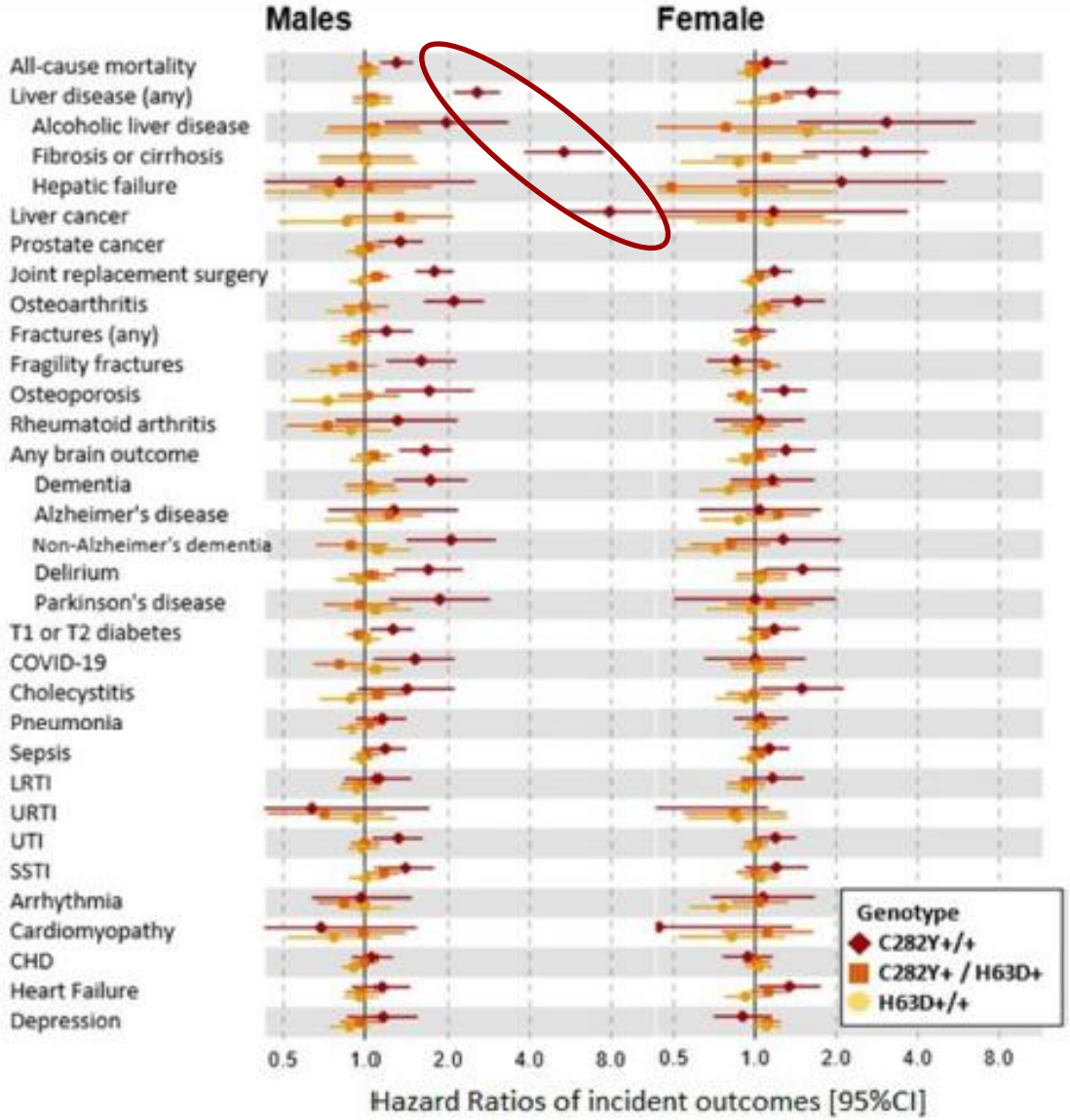
GENETIC (p.C282Y variant)? – LOW CLINICAL PENETRANCE

BMJ Open *HFE* genotypes, haemochromatosis diagnosis and clinical outcomes at age 80 years: a prospective cohort study in the UK Biobank

Mitchell R Lucas,[1] Janice L Atkins ,[1] Luke C Pilling ,[1] Jeremy D Shearman,[2] David Melzer[1]



How to predict?



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What modifies the clinical penetrance of hemochromatosis?

Received: 11 March 2022 | Revised: 11 May 2022 | Accepted: 11 May 2022

DOI: 10.1002/hep.32575

ORIGINAL ARTICLE

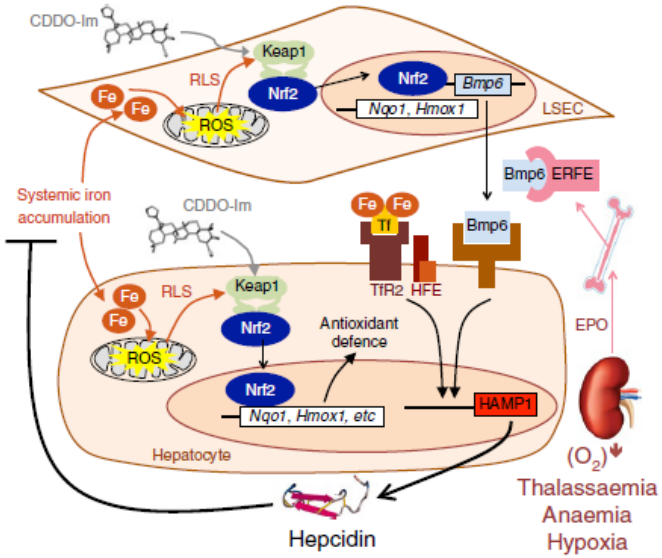
Genetic modifiers of penetrance to liver endpoints in *HFE* hemochromatosis: Associations in a large community cohort

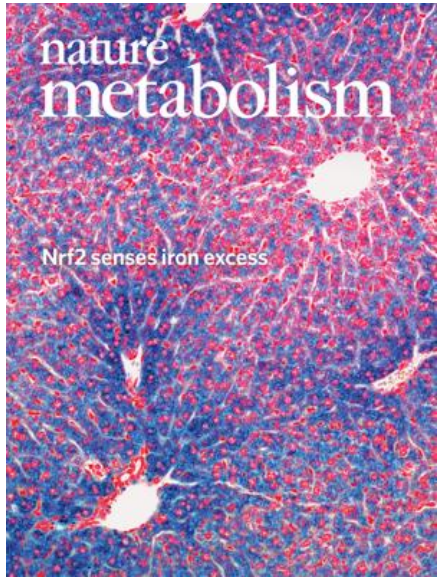
Luke C. Pilling | Janice L. Atkins | David Melzer

"*Overall, the findings show that HFE p.C282Y homozygote penetrance to clinical disease in a large community cohort was modified by population–derived* ***polygenic risk scores for iron measures and for HH-related conditions***"

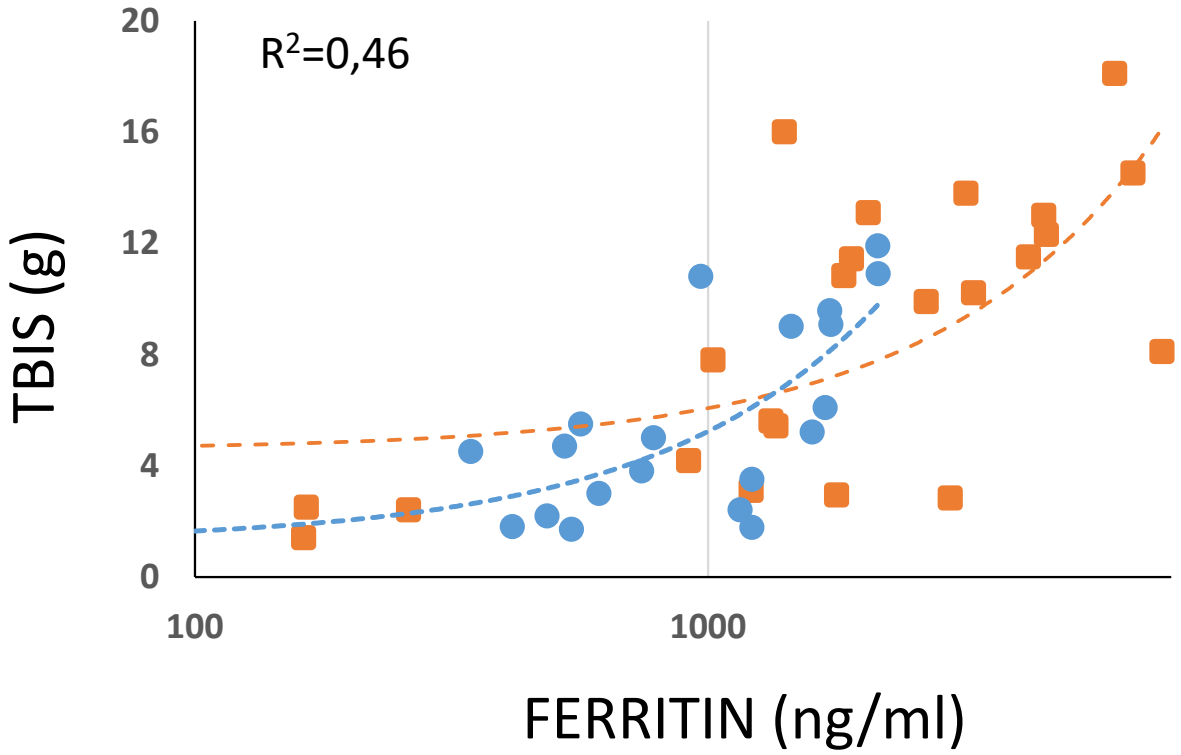
What modifies the clinical penetrance of hemochromatosis?

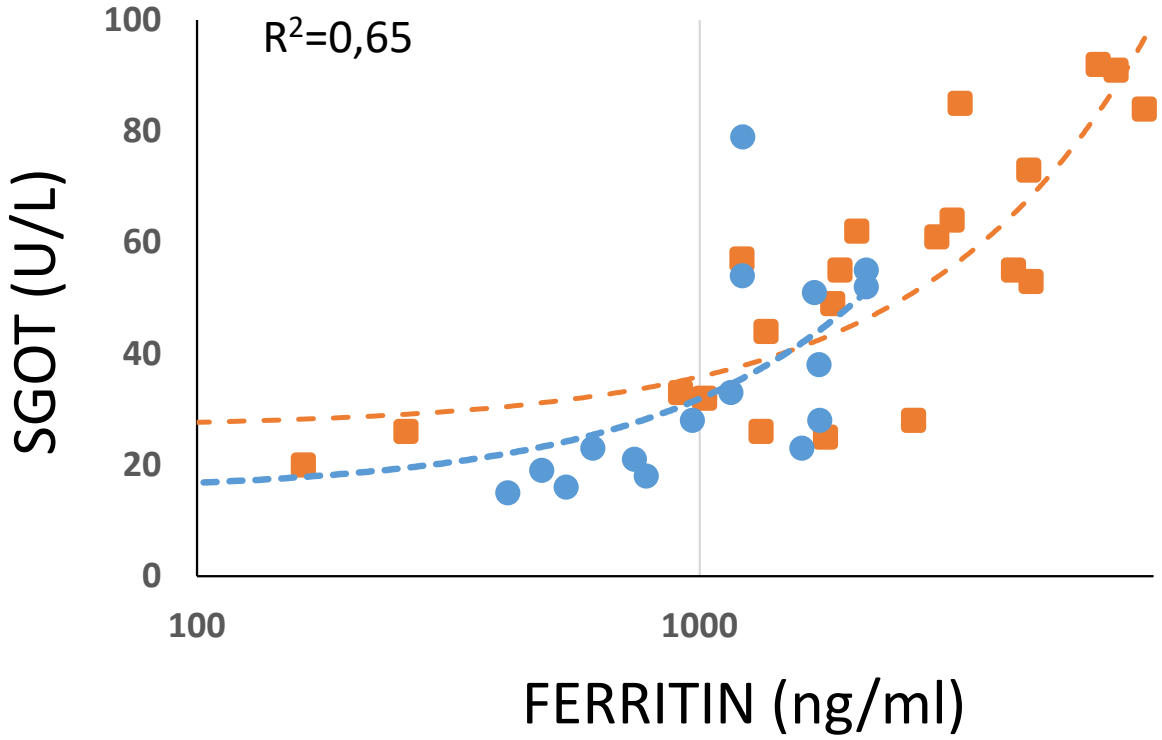
NRF2 senses toxic iron excess and regulates systemic iron levels via BMP6/hepcidin





Lim PJ, Duarte TL, Arezes J, Garcia-Santos D, Hamdi A, Pasricha SR, Armitage AE, Mehta H, Wideman S, Santos AG, Santos-Gonçalves A, Morovat A, Hughes JR, Soilleux E, Wang CY, Bayer AL, Klenerman P, Willberg CB, Hartley RC, Murphy MP, Babitt JL, Ponka P, Porto G, Drakesmith H. 2019 **Nat Metabol**





NRF2 rs35652124 SNP genotype

	Frequency of cirrhosis
TT	5/18 **(25%)**
TC/CC	2/25 **(5%)**

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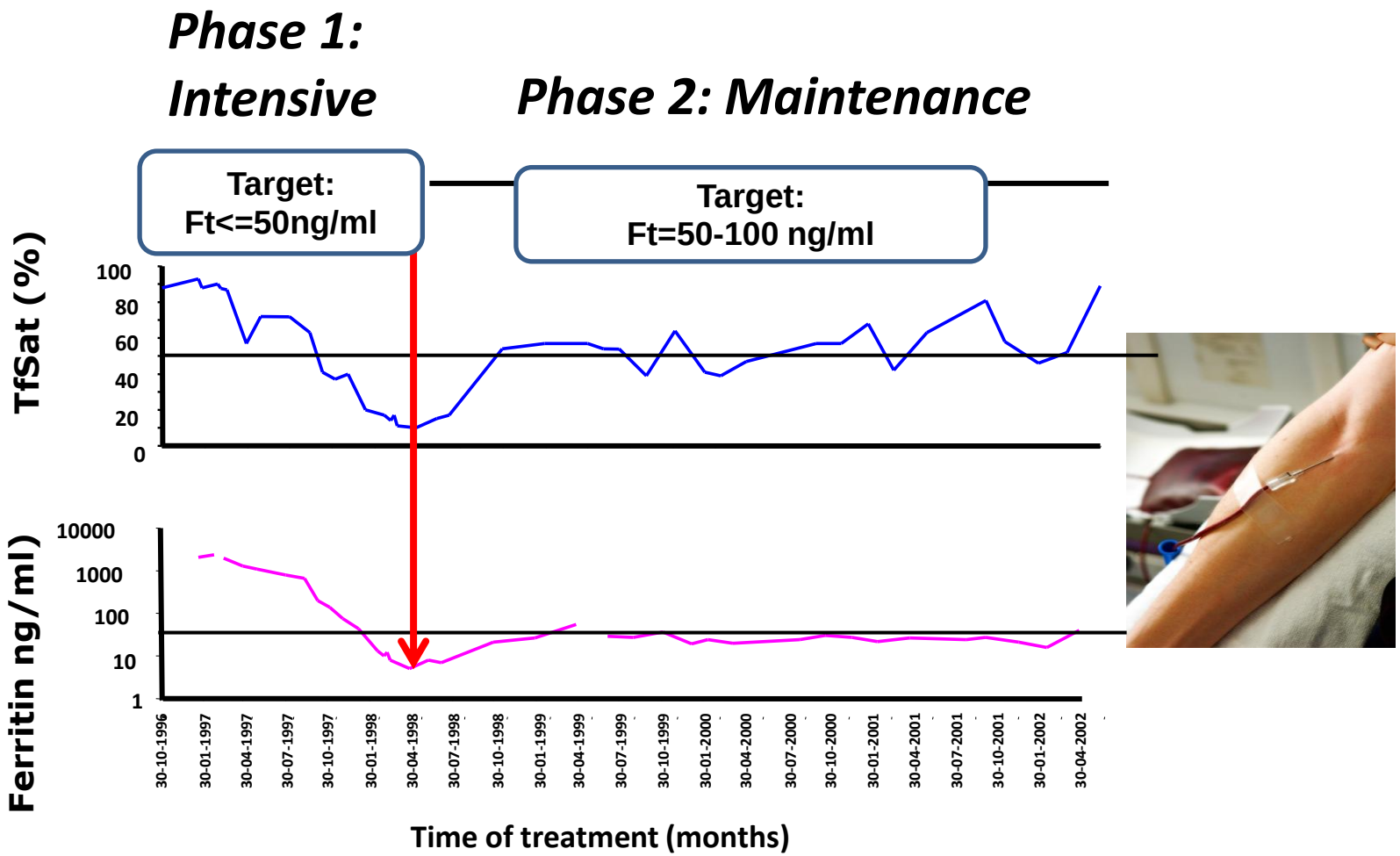
THE HEMOCHROMATOSIS TREATMENT:



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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 19 March 2024
DOI 10.3389/fmed.2024.1362941

OPEN ACCESS

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RECEIVED 29 December 2023
ACCEPTED 07 March 2024
PUBLISHED 19 March 2024

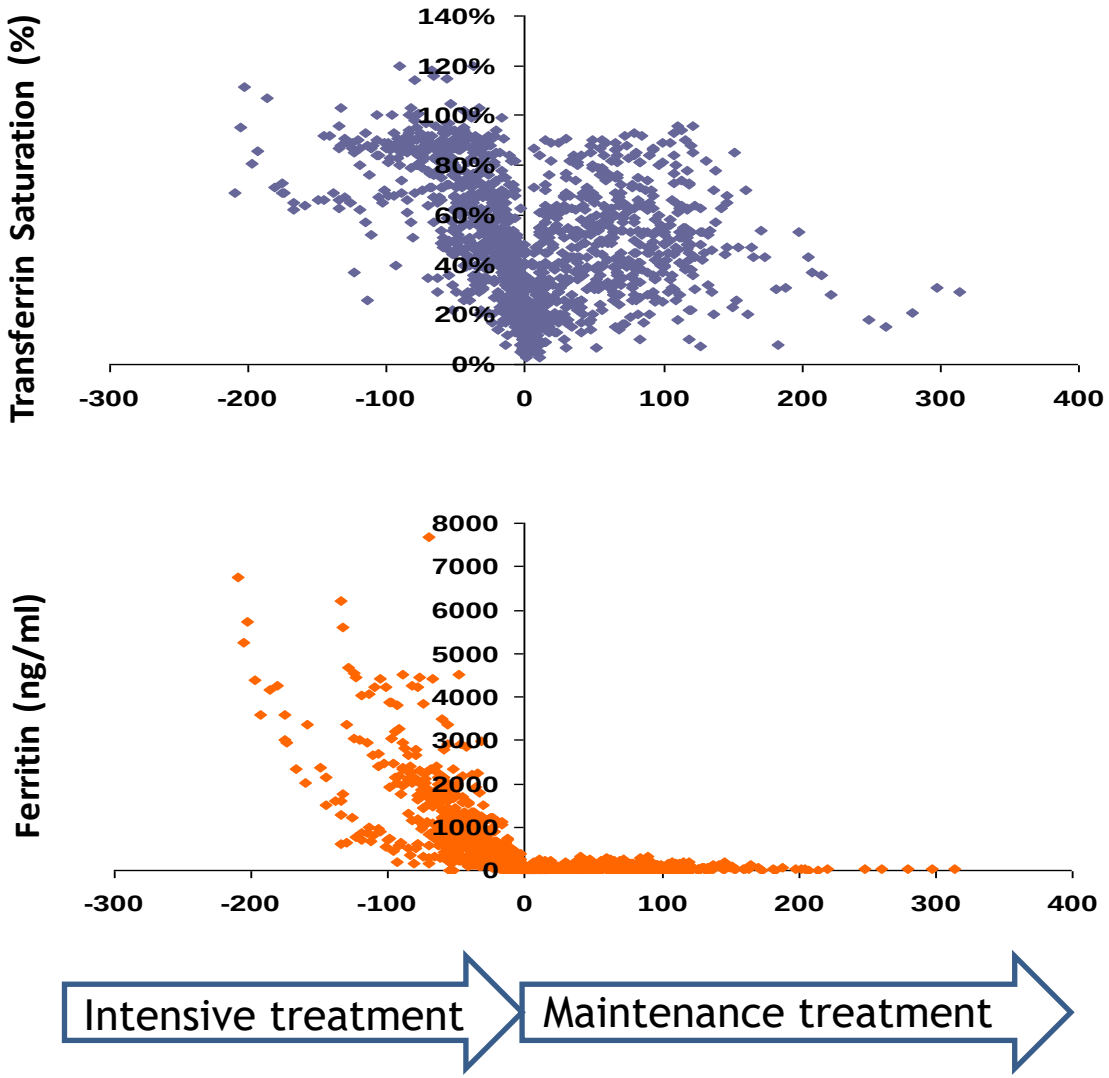
CITATION
Infanti L, Leitner G, Moe M, Pehlic V, Cattaneo M, Benkert P, Holbro A, Passweg J, Worel N and Buser A (2024) Blood donation for iron removal in individuals with HFE mutations: study of efficacy and safety and short review on hemochromatosis and blood donation.
Front. Med. 11:1362941.
doi: 10.3389/fmed.2024.1362941

Blood donation for iron removal in individuals with HFE mutations: study of efficacy and safety and short review on hemochromatosis and blood donation

Laura Infanti[1,2]*, Gerda Leitner[3], Morten Moe[4], Vildana Pehlic[1], Marco Cattaneo[5], Pascal Benkert[5], Andreas Holbro[1,2], Jakob Passweg[2], Nina Worel[6] and Andreas Buser[1,2]

[1]Regional Blood Transfusion Centre Swiss Red Cross Basel, Basel, Switzerland, [2]Division of Hematology, University Hospital, University of Basel, Basel, Switzerland, [3]Austrian Red Cross, Vienna, Austria, [4]Unit of Medical Biochemistry, Division of Diagnostics and Technology, Akershus University Hospital, Akershus, Norway, [5]Clinical Trial Unit, Department of Clinical Research, University and University Hospital Basel, Basel, Switzerland, [6]Department for Transfusion Medicine and Cell Therapy, Medical University Vienna, Vienna, Austria

MONITORING HEMOCHROMATOSIS TREATMENT:



THE COVID19 LOCKDOWN OPPORTUNITY

Hospital Lockdown
March 2020

Resume Day Hospital activity
May 2020

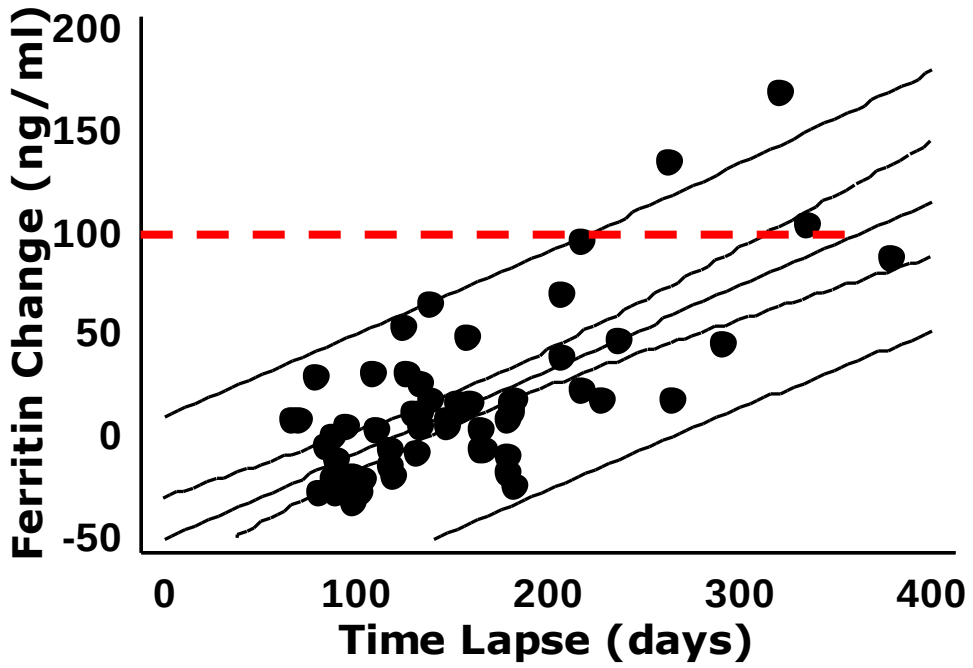
End of study
Feb 2021

Calculated **TIME LAPSE** (nº of days from last phlebotomy)

Coutinho et al. Hemasphere. 2022 Aug 23;6(9):e770.

THE HEMOCHROMATOSIS TREATMENT:

Ferritin increases in hemochromatosis subjects after discontinuing their regular maintenance treatment at a predicted rate of 100ng/ml per year



Coutinho et al. Hemasphere. 2022 Aug 23;6(9):e770.

NOVEL THERAPEUTIC TARGETS?

Casu C, Nemeth E, Rivella S. Hepcidin agonists as therapeutic tools. Blood. 2018;131(16):1790-1794

Classification of hepcidin agonists

Hepcidin agonists	Company	Drug	Target	Clinical trials
Class 1: hepcidin mimetics	University of California, Los Angeles	MHs (PR65, PR73, M009, M012)	Ferroportin	Validated in preclinical studies
	La Jolla Pharmaceutical Company	LJPC-401 (hepcidin formulation)	Ferroportin	Phase 1: no toxicity reported; expected hypoferremia observed
	Protagonist Therapeutics	PTG-300	Ferroportin	Phase 1: no serious adverse events reported; expected hypoferremia observed
Class 2: stimulators of hepcidin production	Ionis Pharmaceuticals	Tmprss6-ASO	Tmprss6	Phase 1 ongoing
	Alnylam Pharmaceuticals	Tmprss6-siRNA	Tmprss6	Validated in preclinical studies
Class 3: ferroportin inhibitors	Vifor Pharma	VIT-2763	Ferroportin	Phase 1 planned in 2018

“The major CHALLENGES in the management of HFE-related hemochromatosis”

1. TO HARMONIZE AND IMPLEMENT AMONG CLINICIANS A CORRECT DIAGNOSIS, CLASSIFICATION AND TREATMENT OF HEMOCHROMATOSIS

2. TO IMPLEMENT STRATEGIES OF POPULATION SCREENING ACCORDING TO NATIONAL REGULATIONS AND DEMONSTRATE RESULTS

3. PROMOTE RESEARCH

“THE RESEARCH TOPICS”

1. PATHOGENESIS OF ARTHROPATHY (implications for treatment)

2. MODIFIERS OF CLINICAL PENETRANCE (implications for screening strategies)

3. FUNDAMENTAL RESEARCH: HFE and iron sensing

Haemochromatosis International

EFAPH Fe

Haemochromatosis patients' research priorities: Towards an improved quality of life. *Romero-Cortadellas L, Venturi V, Martín-Sánchez JC, Toska K, Prince D, Butzeck B, Porto G, Milman NT, Committee HS, Sánchez M. Health Expect. 2023 Dec;26(6):2293-2301*

When analyzing patients' preferences in HC research, they selected *Conduct research into arthritis and joint problems* as the top priority in the hemochromatosis field (45.3%), closely followed by *Promote knowledge about hemochromatosis among medical doctors* (42.5%) and the third most voted choice, *Investigate new or alternative treatments for hemochromatosis* (30%).