Thursdays Webinars

EuroBloodNet

Diagnosis and clinical management of rare forms of Hemochromatosis

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ERN-EuroBloodNet subnetwork Hemochromatosis and other rare genetic disorders of iron metabolism and heme synthesis
Verona – Italy
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of the European Union

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

Conflicts of interest - DG

- *SANOFI-GENZYME (Advisory Board)*
- *SILENCE THERAPEUTICS (Advisory Board)*
- *VIFOR PHARMA (Advisory Board)*
- *NOVARTIS (Advisory Board)*
- *TAKEDA-SHIRE (Lectures)*

(not relevant to this presentation)

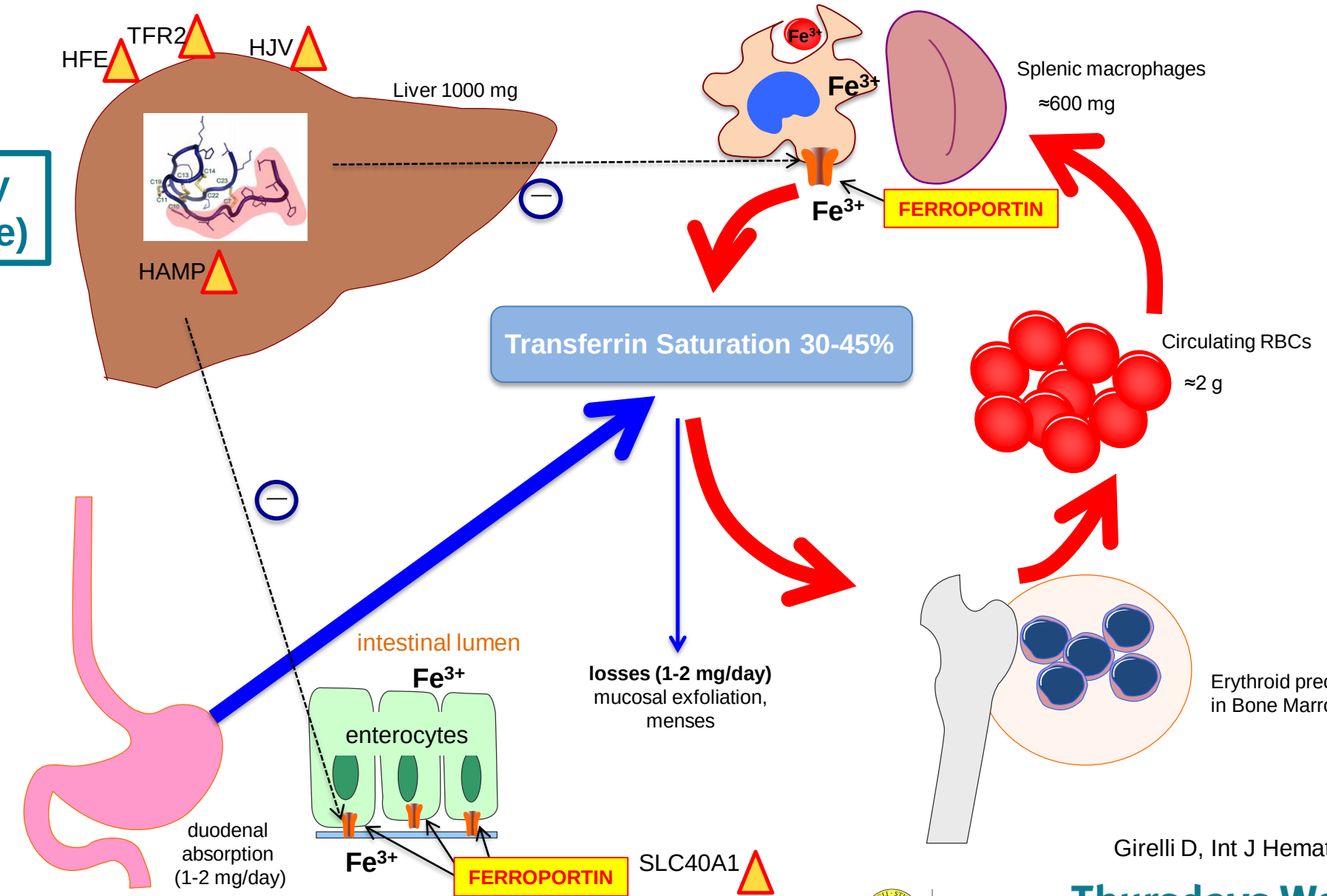
LEARNING OBJECTIVES

1. CLEAR DEFINITION OF (VERY) RARE H. VERSUS CLASSICAL H.
2. DIFFERENTIAL DIAGNOSIS OF RARE H. VERSUS OTHER TYPES OF «UNEXPLAINED» HYPERFERRTINEMIA W/O IRON OVERLOAD
3. TREATMENT OPTIONS

PATHOPHYSIOLOGY OF HEMOCHROMATOSIS

a unique clinical disorder due to mutations in multiple genes

Hepcidin deficiency (rarely H. resistance)



Girelli D, Int J Hematol 2018

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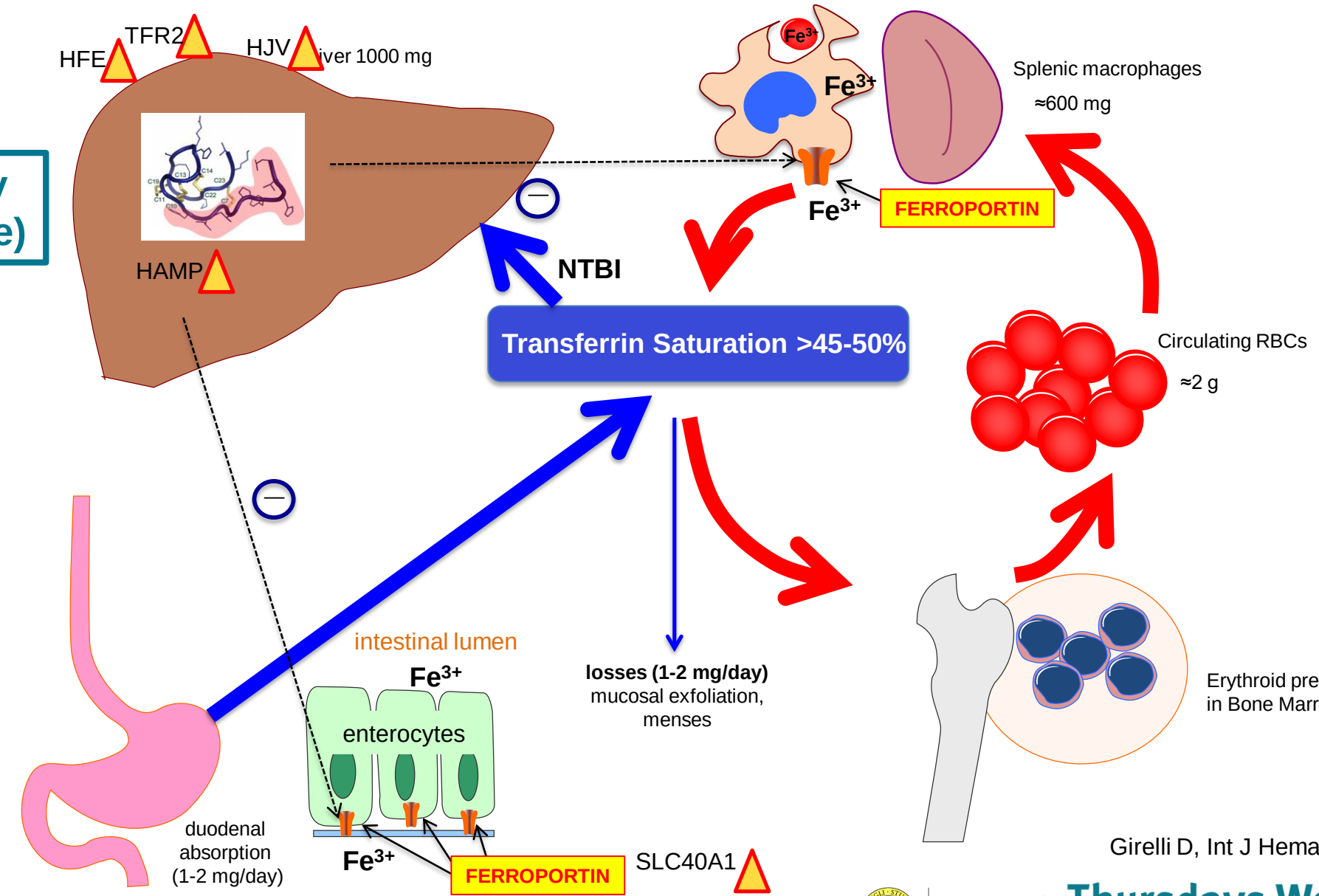

Girelli D, Int J Hematol 2018

PATHOPHYSIOLOGY OF HEMOCHROMATOSIS

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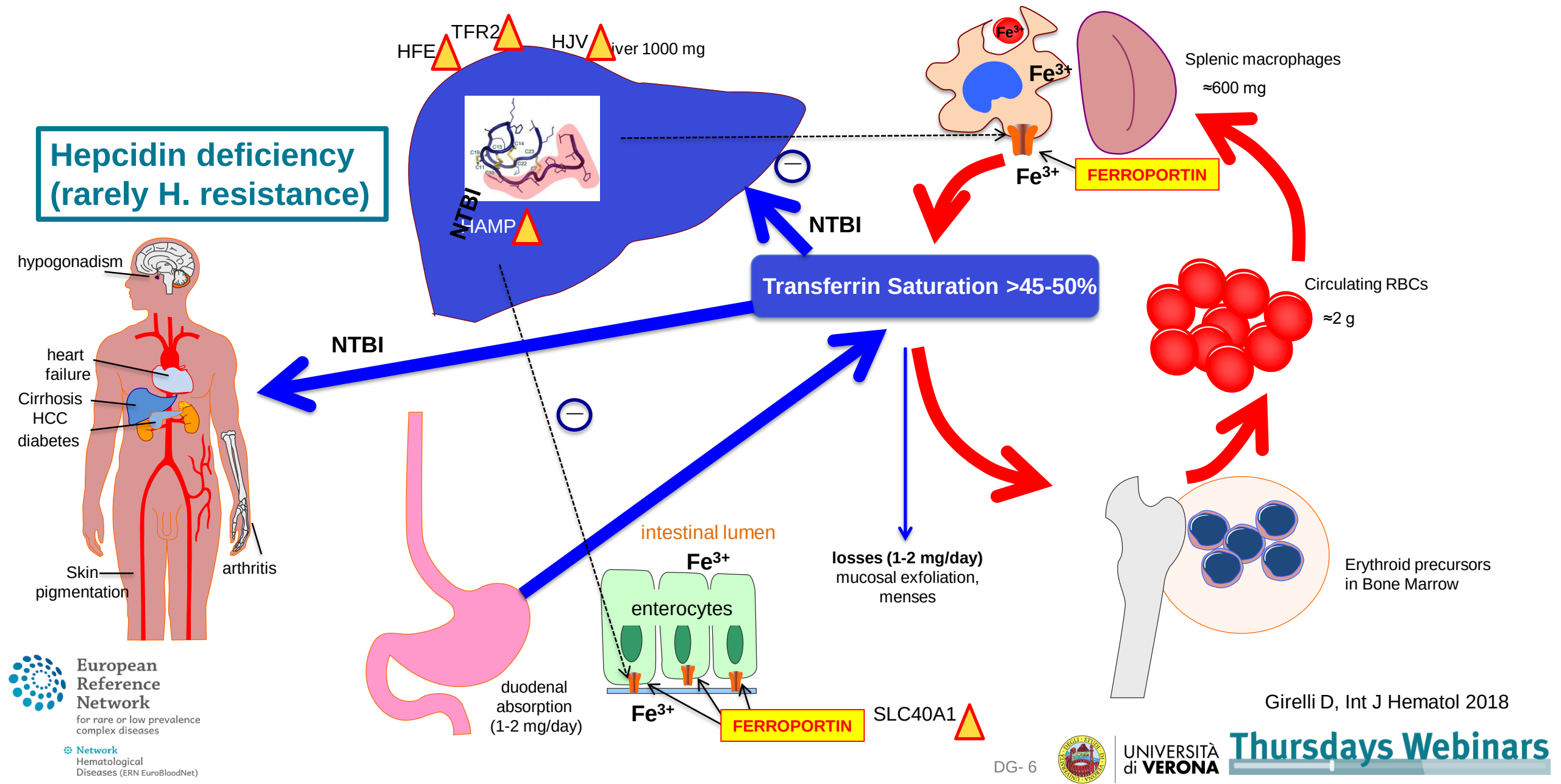

Girelli D, Int J Hematol 2018

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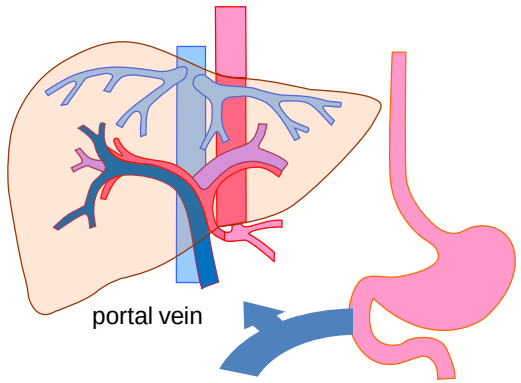
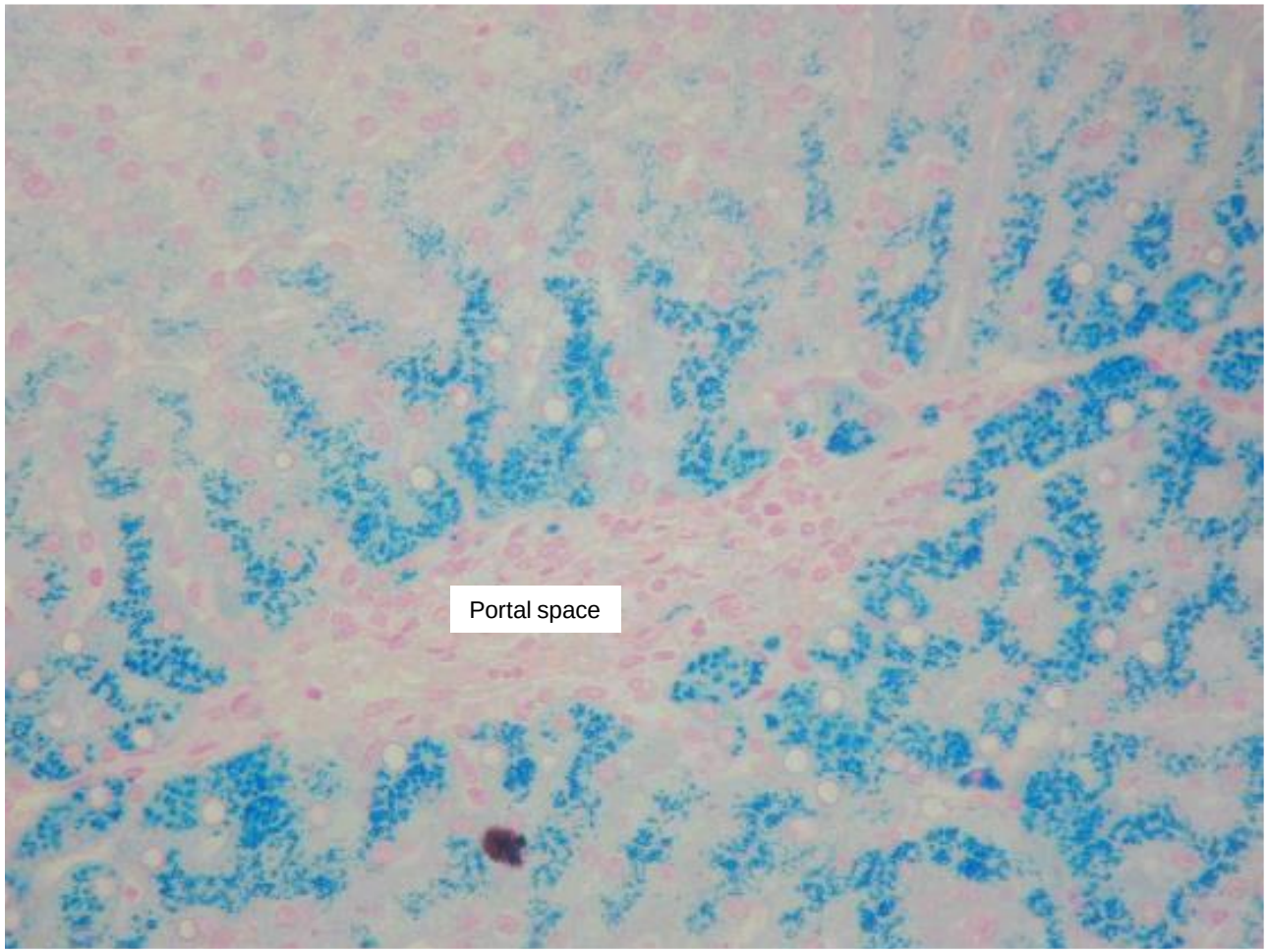
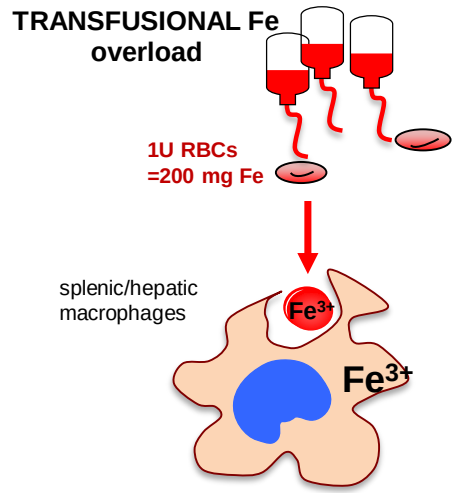
Liver iron deposition (by Perls Prussian blue stain) in H. is (initially) in periportal hepatocytes



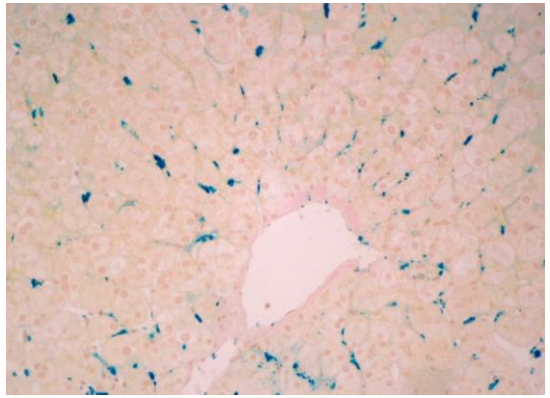
duodenal Fe hyperabsorption



Girelli D, Gastroenterology 2002

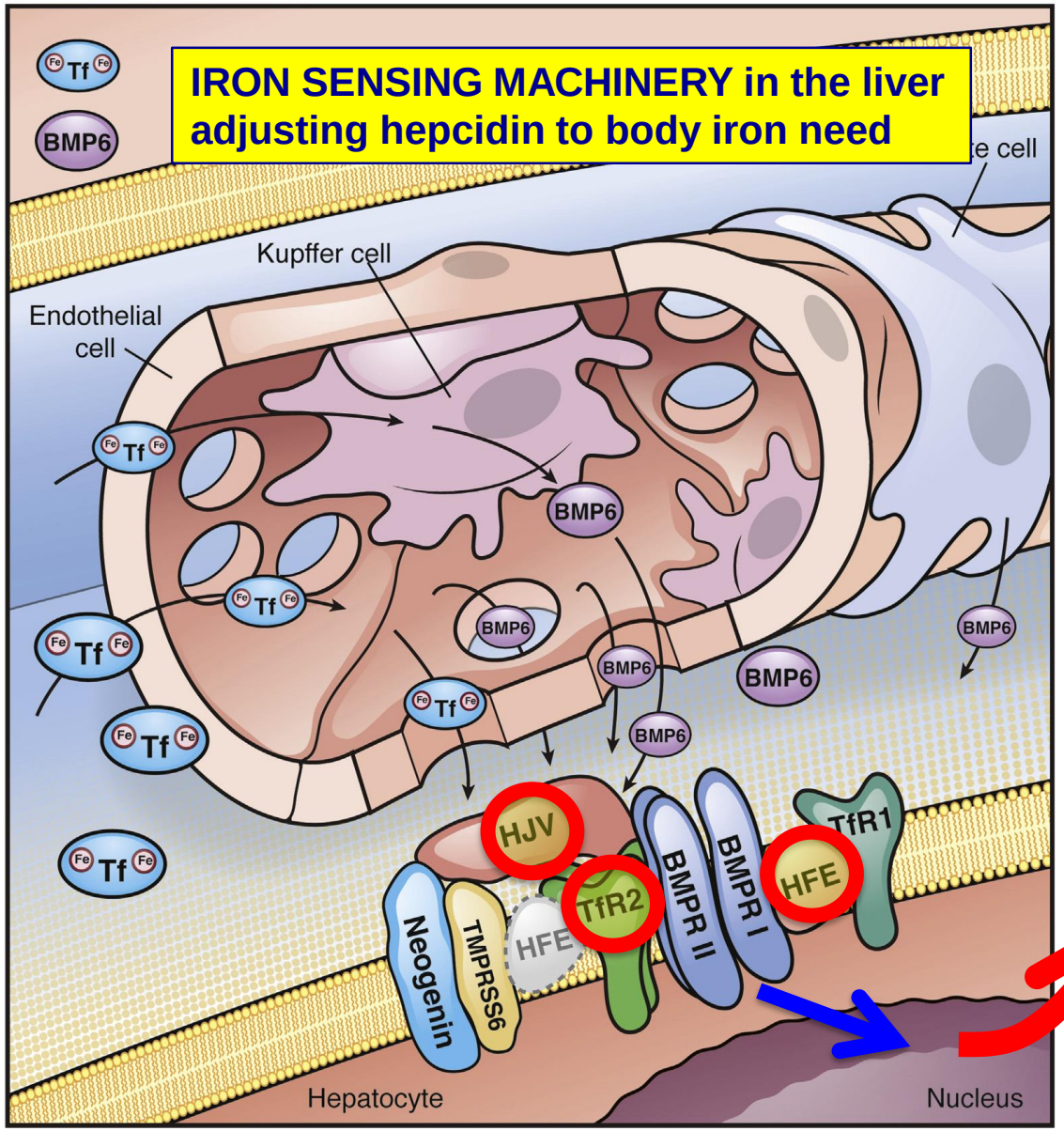


Prevalent iron staining of **Kupffer cells** (in a well-chelated **β-TM** pt.)



Origa R, Haematologica 2007

H. IS A GENETICALLY HETEROGENOUS DISORDER

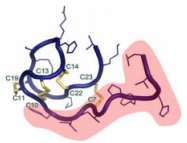


Mutations in any of the genes encoding proteins of liver iron sensing machinery (***HFE***, ***TFR2***, ***HJV***)…

…or also in the genes encoding for hepcidin (***HAMP***)
… or ferroportin (***SLC40A1****):

****GoF*** on → **hepcidin-resistance**
LoF → different phenotype (**FD**)

hepcidin transcription



Pietrangelo A, Gastroenterology 2015

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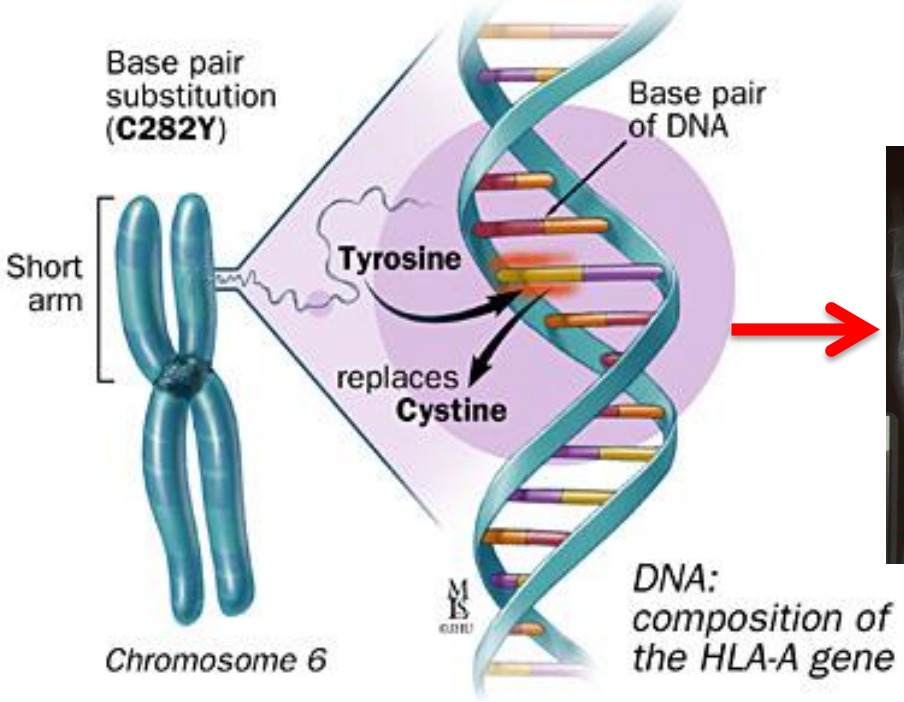
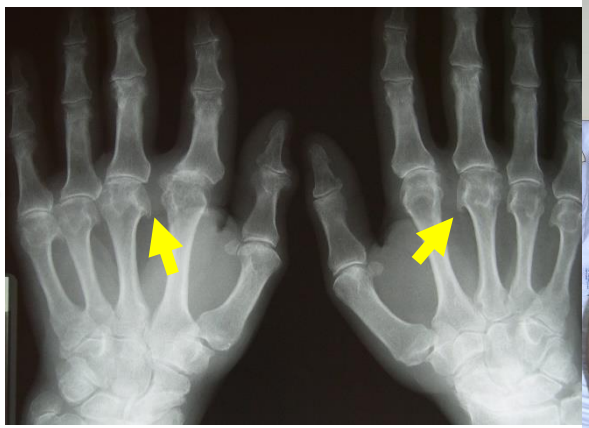
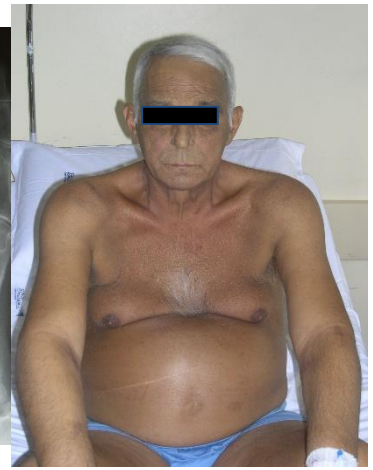
CLASSICAL H. DUE TO C282Y HOMOZYGOSITY (HFE GENE)





ARTHROPATHY



BRONZE DIABETES AND CIRRHOSIS

1. **LOW PENETRANCE**
   (highly influenced by cofactors e.g. alcohol)
2. **MIDDLE-AGE ONSET WITH SUBSTANTIAL MALE PREVALENCE**
   (F. affected only after cessation of menses)
3. **CAUCASIANS POPULATIONS**
   ("celtic" origin ~ 4,000 years ago in Ireland)
4. **EASY DIAGNOSIS**
   (wide availability of first level genetic test for classical HFE mutations)

FEATURES OF RARE FORMS OF H.

1. Worldwide distribution in different ethnicities (EU immigrants!)
2. Possible early-onset with high penetrance and M:F 1:1 (“juvenile” forms)
3. Severe phenotype, more often including heart failure, hypogonadism, diabetes (“juvenile” forms)
4. Complex molecular diagnosis (mutations in non-HFE genes typically private, requiring sequencing and adequate interpretation)

"TYPE-NUMERIC" HEMOCHROMATOSIS NOMENCLATURE

Type 1: *HFE*-haemochromatosis (*HFE*-related)

- Type 1a: Cys282Tyr homozygosity.
- Type 1b: compound Cys282Tyr/His63Asp heterozygosity. This usually only occurs when associated comorbidities exist.
- Type 1c: other *HFE* genotypes—eg, Ser65Cys, etc. These mutations do not substantially affect the phenotype.

Type 2: Haemochromatosis (non-*HFE*-related)

- Type 2a: juvenile haemochromatosis (haemojuvelin mutations).
- Type 2b: juvenile haemochromatosis (hepcidin mutations).

Type 3: Mutated transferrin receptor 2

Type 4: Mutated ferroportin 1 gene, *SLC40A1*

Powell LP, Lancet 2016

H. nomenclature: update and recommendations

BIOIRON
International Society for the Study of Iron in Biology and Medicine

HFE-related	p.Cys282Tyr homozygosity
Non *HFE*-related	Rare pathogenic variants in "*non-HFE*" genes: - *HJV*-related - *HAMP*-related - *TFR2*-related - *SLC40A1* (GOF)
Digenic	Compound heterozygosity for mutations in two different genes involved in iron metabolism (*HFE* and/or non-*HFE*)
Molecularly undefined	Molecular characterization (still) not available after sequencing of known genes (provisional diagnosis)

manuscript in preparation

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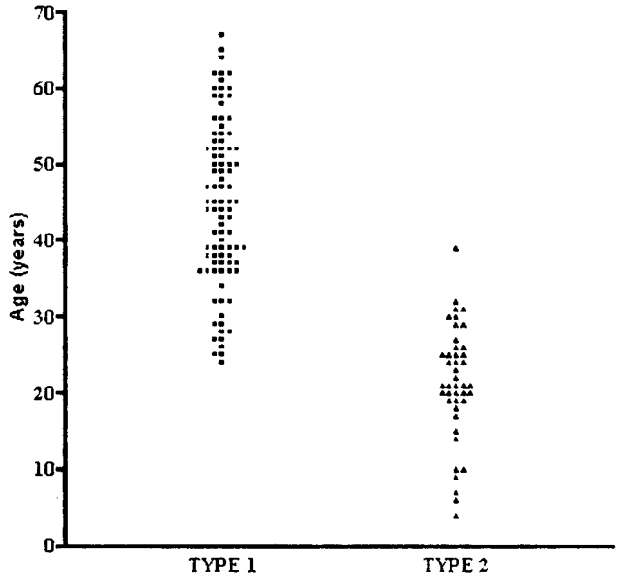
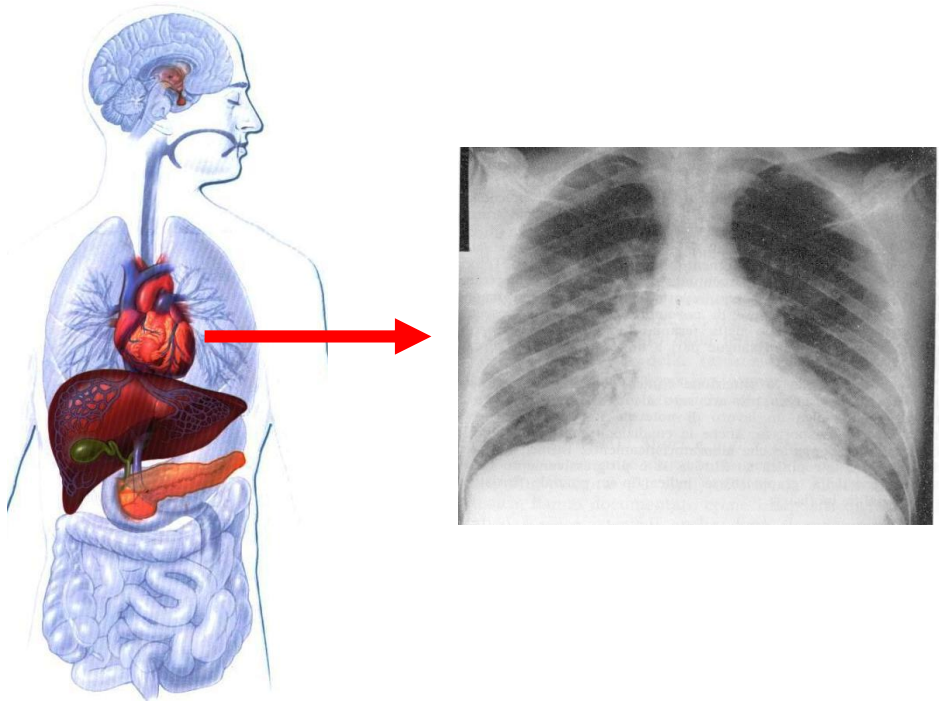
“JUVENILE” HEMOCHROMATOSIS

Well defined clinical form (known since 1950’s)* characterized by:

- ✓ Early onset (usually II decade; exceptions can occur)
- ✓ Full penetrance, severe multi-organ damage
- ✓ Both genders equally affected (no male predominance)
- ✓ Negligible contribute of acquired cofactors



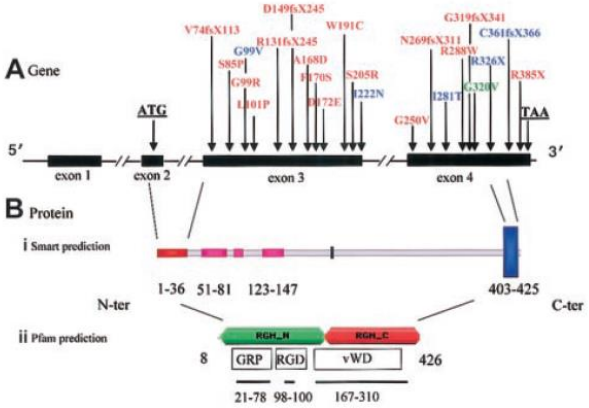
Camaschella C, Semin Hematol 2002



*Nussbaum T, J Genet Hum 1951

Molecular basis of juvenile hemochromatosis (HJV or HAMP mutations)

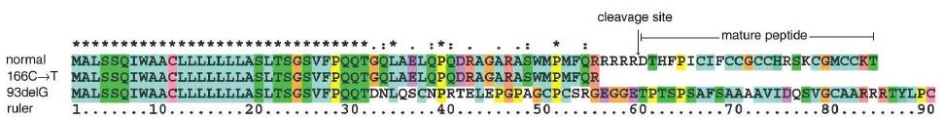
- ✓ most frequently due to ***HJV*** mutations (~90%).

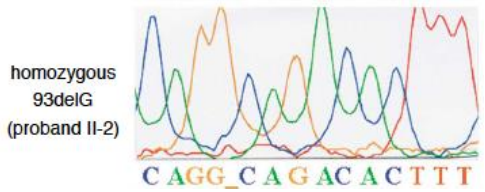


Lanzara C, Blood 2004

- ✓ One recurrent mutation G320V (present in ≈ 50% cases)

- ✓ Very rarely due to mutations of the gene encoding hepcidin itself (***HAMP***)





Roetto A, Nat Genet 2003

Table 1 | Mutations of the *HJV* gene linked to JH.

Residue mutation	Exon	Type of mutation	Nucleotide change	Family origin	References
Q6H	2	Missense	18G > C	Asian	Huang et al., 2004
L27fsX51	2	Frame shift	81delG	English/Irish	Wallace et al., 2007
R54X	3	Nonsense	160A > T	African American	Murugan et al., 2008
G66X	3	Nonsense	196G > T	Romanian	Jánosi et al., 2005
V74fsX113	3	Frame shift	220delG	English	Lanzara et al., 2004
C80R	3	Missense	238T > C	Caucasian	Lee et al., 2004
S85P	3	Missense	253T > C	Italian	Lanzara et al., 2004
G99R	3	Missense	295G > A	Albanian	Lanzara et al., 2004
G99V	3	Missense	296G > T	Multiple	Papanikolaou et al., 2004; Silvestri et al., 2007
L101P	3	Missense	302T > C	Albanian	Lanzara et al., 2004; Lee et al., 2004
G116X	3	Nonsense			Santos et al., 2012
C119F	3	Missense	G356 > T	German	Gehrke et al., 2005; Silvestri et al., 2007
R131fsX245	3	Frame shift	391-403del	Italian	Lanzara et al., 2004
D149fsX245	3	Frame shift	445delG	Italian	Lanzara et al., 2004
L165X	3	Nonsense	494T > A		van Dijk et al., 2007
A168D	3	Missense	503C > A	Australian /English	Lanzara et al., 2004
F170S	3	Missense	509T > C	Italian	De Gobbi et al., 2002; Lanzara et al., 2004; Silvestri et al., 2007
D172E	3	Missense	516C > G	Italian	Lanzara et al., 2004
R176C	3	Missense	526C > T	European	Aguilar-Martinez et al., 2007; Ka et al., 2007
W191C	3	Missense	573G > T	Italian	De Gobbi et al., 2002; Lanzara et al., 2004; Silvestri et al., 2007
N196K	3	Missense	588T > G		Santos et al., 2012
S205R	3	Missense	615C > G	Italian	Lanzara et al., 2004
I222N	4	Missense	665T > A	Canadian	Papanikolaou et al., 2004
K234X	4	Nonsense	700-703AAG del	European	Santos et al., 2012
D249H	4	Missense	745G > C	Asian	Santos et al., 2012
G250V	4	Missense	749G > T	Italian	Lanzara et al., 2004
N269fsX311	4	Frame shift	806 > 807insA	English	Lanzara et al., 2004
I281T	4	Missense	842T > C	Multiple	Huang et al., 2004; Papanikolaou et al., 2004
C282Y	4	Missense		Caucasian	Le Gac et al., 2004
R288W	4	Missense	863C > T	French	Lanzara et al., 2004
R288Y	4	Missense	862C > T		Wallace et al., 2007
E302K	4	Missense	904G > A	Brazilian	Santos et al., 2011
A310G	4	Missense	929C > G	Brazilian	de Lima Santos et al., 2010; Santos et al., 2011
Q312X	4	Nonsense	934C > T	Asian	Nagayoshi et al., 2008
G319fsX341	4	Frame shift	954-955insG	Italian	Lanzara et al., 2004
G320V	4	Missense	959G > T	Multiple	Lanzara et al., 2004; Papanikolaou et al., 2004; Gehrke et al., 2005; Silvestri et al., 2007; Santos et al., 2011
C321W	4	Missense	963C > G	European	Wallace et al., 2007
C321X	4	Nonsense	962G > A, 963C > A	Asian	Huang et al., 2004; Santos et al., 2012
R326X	4	Nonsense	976C > T	Asian	Huang et al., 2004; Papanikolaou et al., 2004
S328fsX337	4	Frame shift	980-983 delTCTC	Slovakian	Gehrke et al., 2005
R335Q	4	Missense	1004G > A		Wallace et al., 2007
C361fsX366	4	Frame shift	1080delC	European	Papanikolaou et al., 2004
N372D	4	Missense	1114A > G		Wallace et al., 2007
R385X	4	Nonsense	1153C > T	Italian	Lanzara et al., 2004; Santos et al., 2012

Core AB, Front Pharmacol 2014

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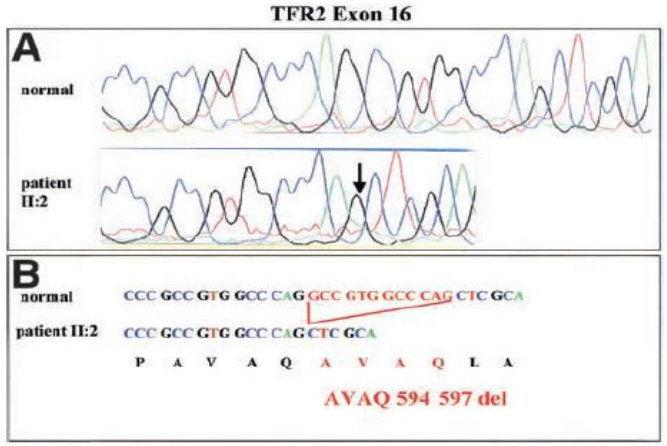
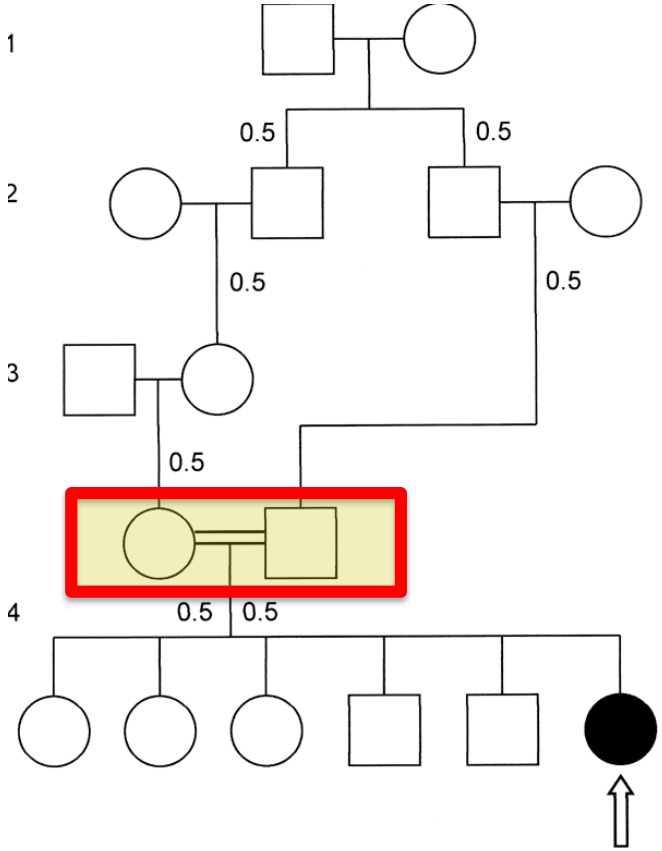
TRANSFERRIN RECEPTOR 2 (TFR2) RELATED HEMOCHROMATOSIS

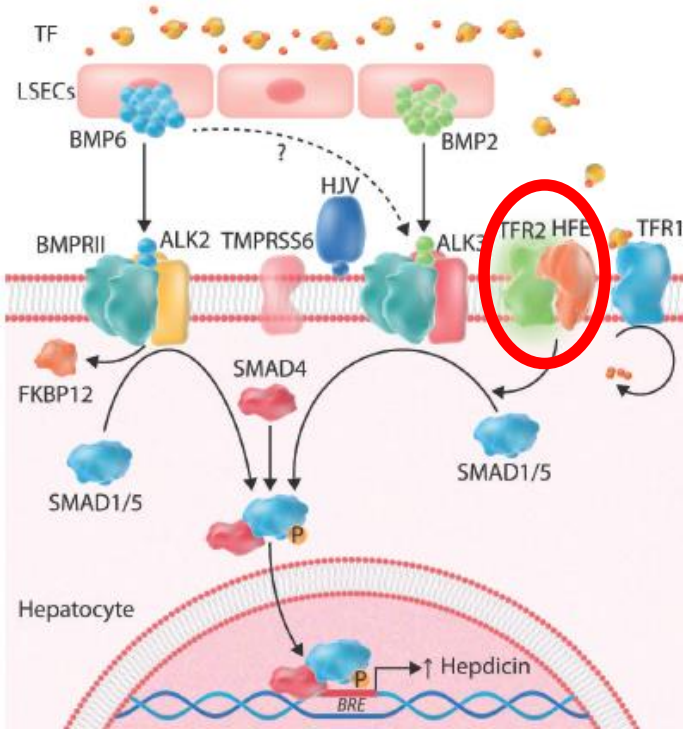
Transmembrane receptor with lower affinity for diferric TF than TFR1, but able to bind HFE in high iron status to promote hepcidin synthesis

Clinical phenotype similar to classical H., but a **tendency to earlier presentation** and often detected in families with **consanguinity**.



Girelli D, Gastroenterology 2002





Camaschella C, Haematologica 2020

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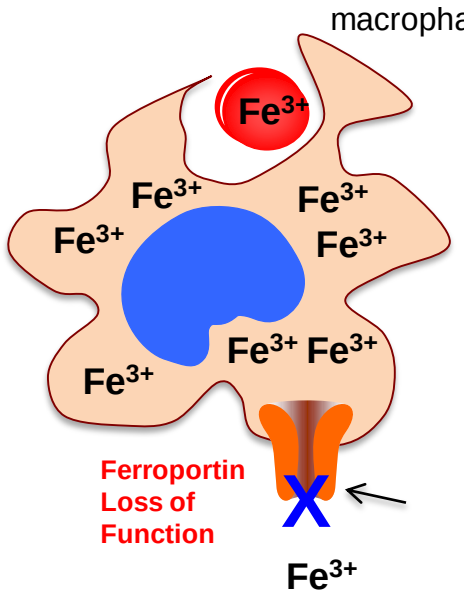
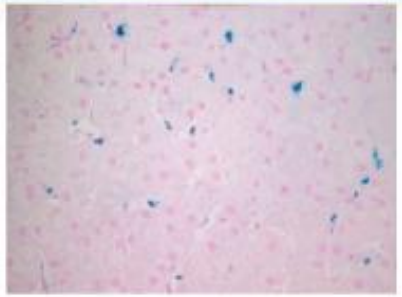
MUTATIONS IN FERROPORTIN GENE* (*SLC40A1*): LoF vs. GoF



Ferroportin disease

Reduced ferroportin activity mainly in tissue macrophages

Iron retention in macrophages



"Kupffer cell iron loading pattern" of an FD patient (pVal162del FPN1 loss of function mutation)

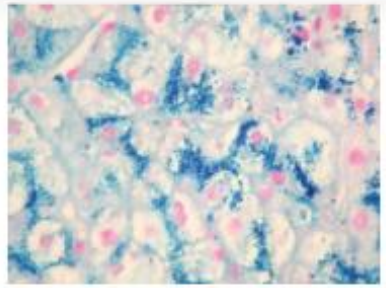
Low/normal serum iron
High serum ferritin

Marginal iron restricted erythropoiesis and clinically mild phenotype

FPN-associated hemochromatosis

Increased ferroportin activity in enterocytes and macrophages

Iron overload in parenchymal cells



"Hepatocellular iron loading pattern" with iron-spared Kupffer cells of FPN1-associated HC patient (p.A69T FPN1 gain-of-function-mutation)

High serum ferritin
(high serum iron)

Iron-driven oxidant stress and damage and mild-to-severe clinical phenotype

*Dominant inheritance!

Very rare genetic disorders of iron metabolism according to clinical presentation

↑ Ferritin, ↑↑ TSAT

Non-HFE Hemochromatosis
(*HJV*, *HAMP*, *TFR2*, *FPN1*^{GoF})

↑ Ferritin, ↑/n TSAT, + ANEMIA

rare anemias due to genetic defect of iron metabolism (*DMT-1*, *TF*, *STEAP3*), **non-syndromic sideroblastic anemias** (*XLSA*, *SLC25A38*, *GLRX5*), **Aceruloplasminemia** (*CP*)*, **Gaucher disease** (*GBA*)

↑↑ Ferritin, n/↓ TSAT

Ferroportin Disease (*FPN1*^{LoF})
Hyperferritinemia (±) Cataract Syndrome (*FL*)
Aceruloplasminemia (*CP*)*

Prevalent neurological symptoms*

rare neurodegenerative disorders "NBIA" (*PKAN*, *PLA2G6*, *C19ORF12*, *WDR45*, *FA2H*, *ATP13A2*, *FL*), **syndromic sideroblastic anemias** (*ABCB7*, *PUS1*, *YARS2*, *MTAPT6*, *TRNT1*)

*anemia lacking in 20% of aceruloplasminemia
*aceruloplasminemia also presents with neurological symptoms, while often preceded by hyperferritinemia and mild anemia

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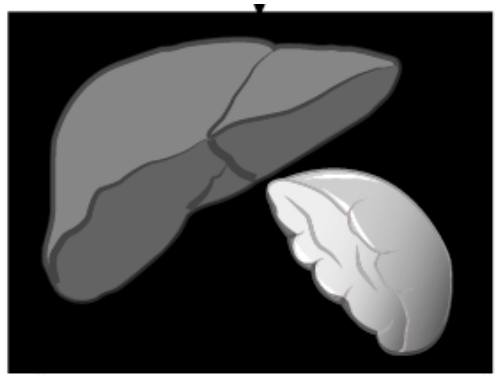
When to consider a rare form of hemochromatosis (diagnosis of exclusion)

1. Clinical and/or biochemical (↑ Ferritin ***and*** ↑ TSAT, no anemia) phenotype resembling the classic form
2. Evidence of IO: ↑ LIC documented by MRI ("black liver and white spleen" pattern) or liver biopsy (with prevalent hepatocyte overload)
3. Negative (or non-diagnostic, e.g. H63D +/-) 1st level genetic test for H.
4. No alternative explanation for IO



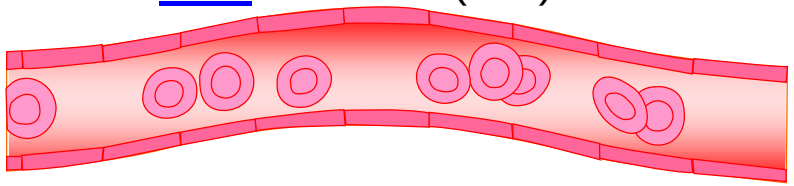
Brissot P, J Hepatol 2016

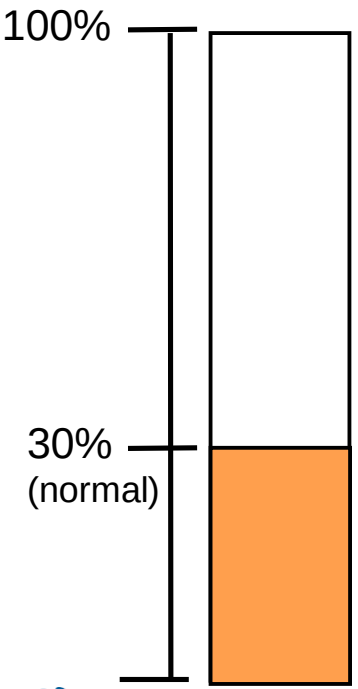
Differential diagnosis of “unexplained” hyperferritinemia (clinical!)

Commonest reason for consultation

5 PILLARS

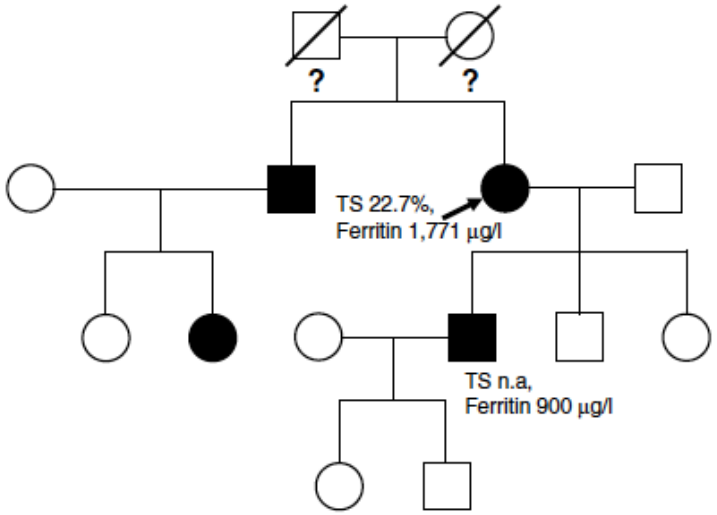
CBC: Anemia? (Y/N)



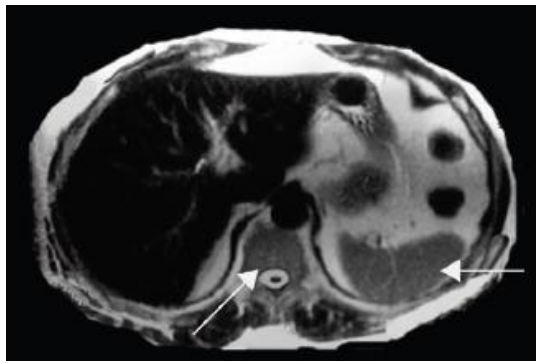


TSAT:
>45%? (Y/N)

Transmission of hyperferritinemia in family study:
Dominant? (Y/N)



Girelli D, J Hepatol 2008



Pietrangelo A, Haematologica 2017

MRI:
↑ LIC? (Y/N)
≠ Fe distribution?

Girelli D, Gastroenterology 2003

Liver biopsy:
(limited indications if ↑ AST/ALT or SF >1,000 µg/l)
↑ LIC? (Y/N)
cellular Fe distribution?
(e.g. periportal hepatocytes→ HH
(Kupffer cells→ FD)
(staging/prognosis)

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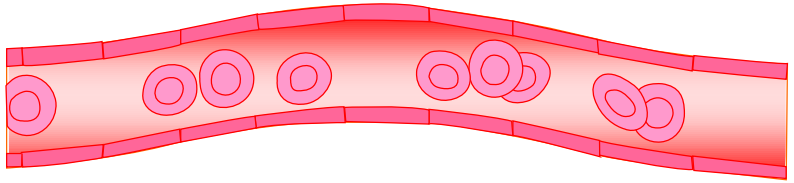
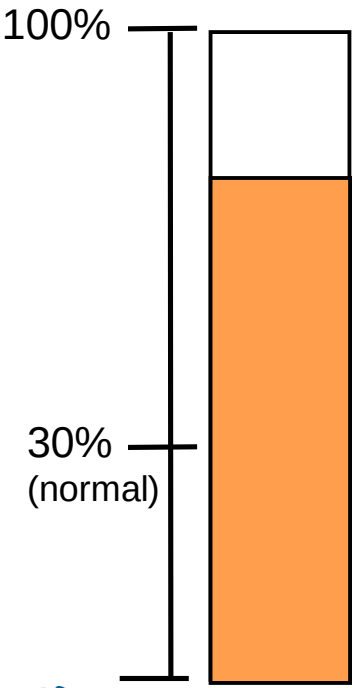
WHEN THINK ABOUT A RARE FORM OF HEMOCHROMATOSIS

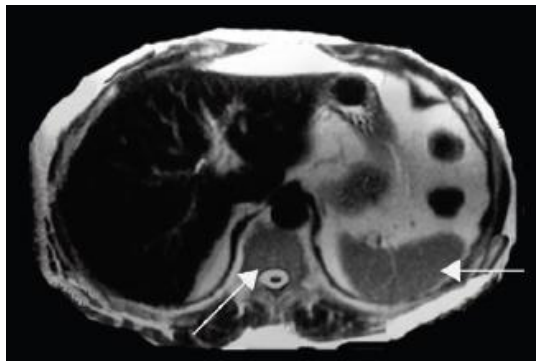
NO Anemia





↑ **TSAT**: >45-50%

Transmission
in family study:
recessive
(no evidence of "dominant hyperferritinemia")



↑ **LIC**
"black liver/white spleen pattern"

↑ **LIC** prevalent in hepatocytes

1st level genetic test negative or not diagnostic

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UNIVERSITÀ di VERONA Thursdays Webinars

MOLECULAR CHARACTERIZATION OF RARE FORM OF H.

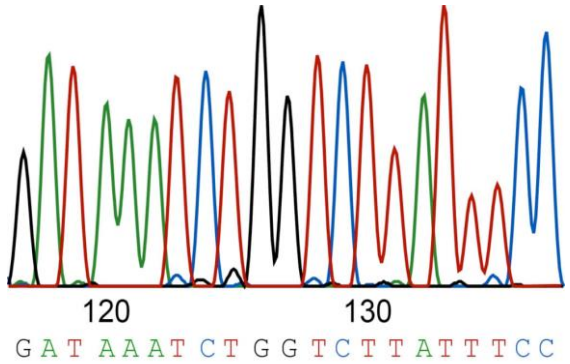
Address the patient to a Referral Center
(and family members for genetic counseling)

Ask for expert opinion through telemedicine (e.g. the EuroBloodNet Clinical Patient Management System CPMS at http://eurobloodnet.eu/cpms/how-to-use-the-cpms/

Send blood samples for DNA analysis to a Referral Center

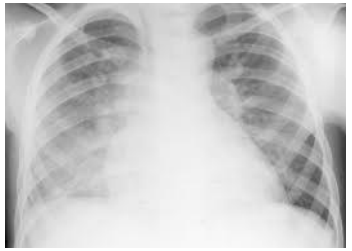
The traditional approach for molecular diagnosis (MD) of non-classical HH

- **Sanger sequencing** of known HH genes
- **Stepwise prioritization** of candidate gene(s) according to clinical clues, e.g.:



- ***TFR2*** in **Mediterranean** areas or in **non-Caucasians**, especially if there is an history of **consanguinity**.

- ***HJV*** (± ***HAMP***) in **juvenile** severe forms



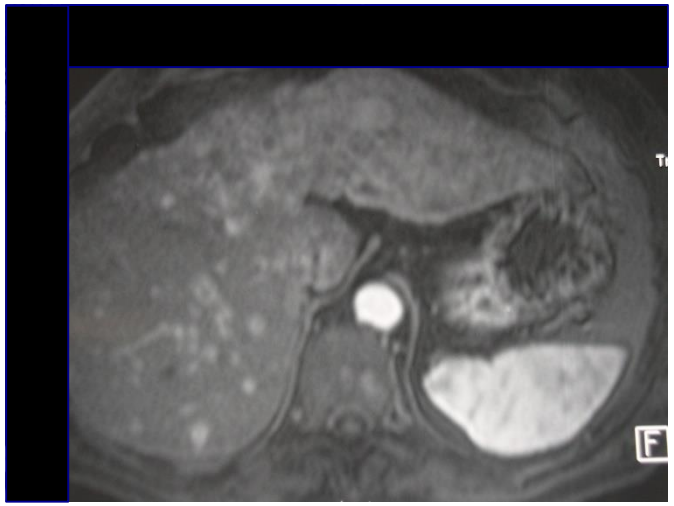
Note: MD could take time and does not influence treatment, don't wait for the result!

Traditional Sanger approach: disadvantages

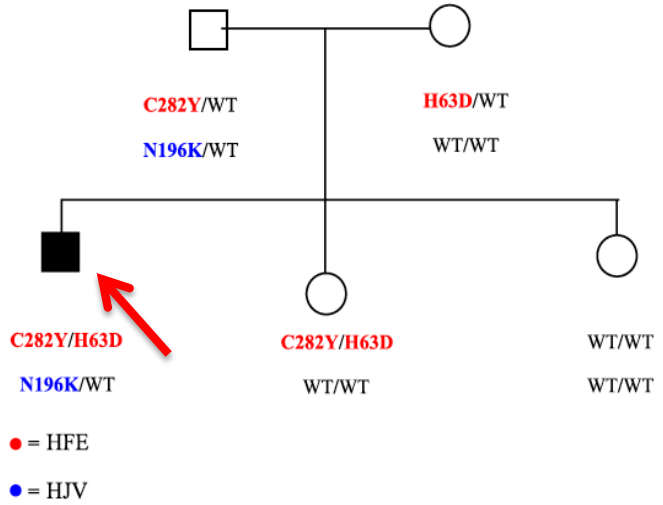
Relatively cumbersome and time-consuming (esp. if prioritized genes turnaround negative)

Potentially overlooks **digenic inheritance** (several case described)

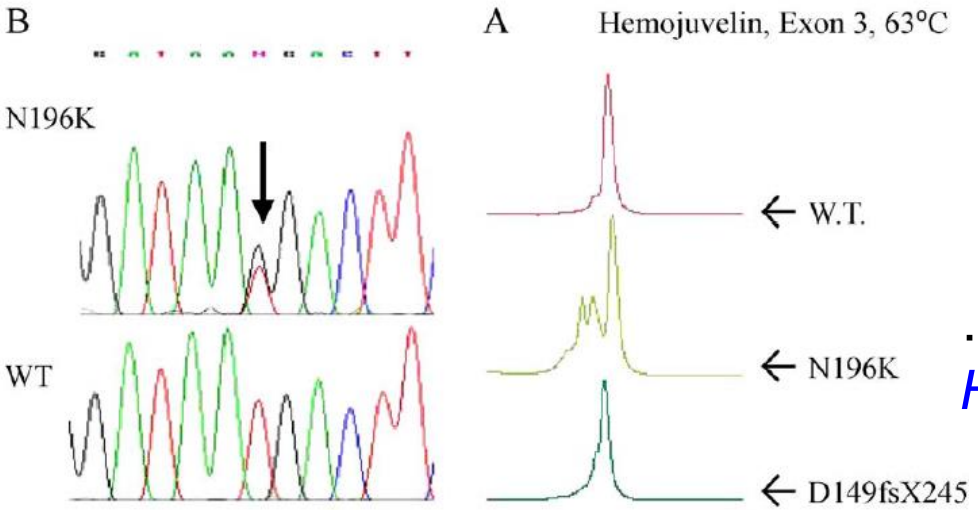
41 year-old male died because of liver cirrhosis and HHC (+ bronze hyperpigmentation and diabetes). 1st level genetic test: *HFE* C282/H63D compound heterozygosity…



Biasiotto G, Blood Cells Mol Dis 2004



Re-sequencing for research purposes



… plus
HJV N196K heterozygosity

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NGS approaches

1. **Targeted NGS**: simultaneous sequencing of the genes of interest (typically ≈10-50 genes, selectively captured by enrichment techniques).

2. **Whole Exome Sequencing (WES):** virtual panels (analyses restricted to the genes of interest).

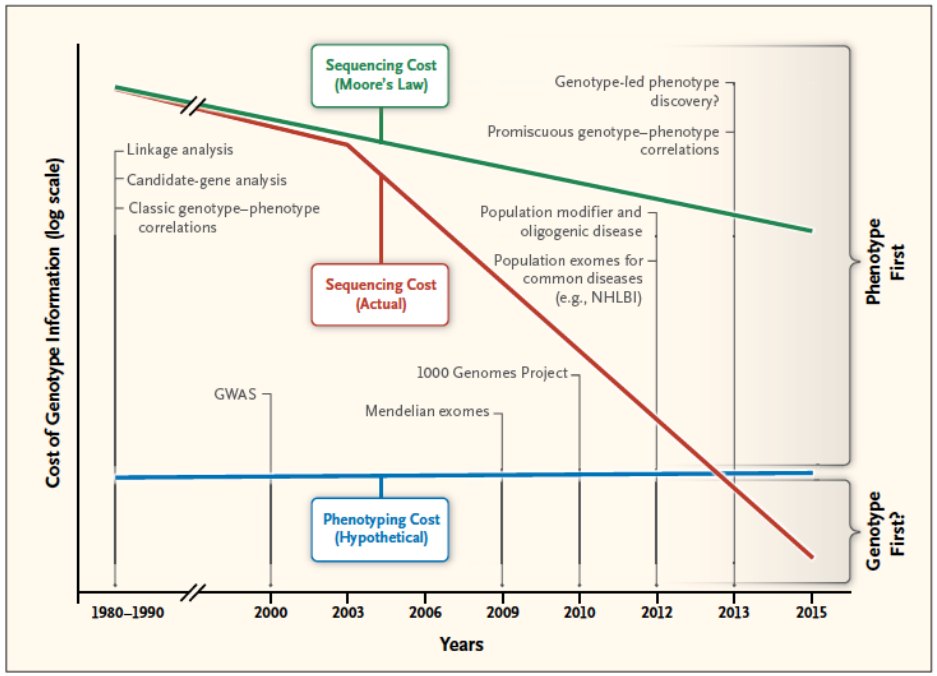
Costs of technologies constantly ↓

ADVANTAGES:

- excellent sensitivity in detecting SNVs or small indels.

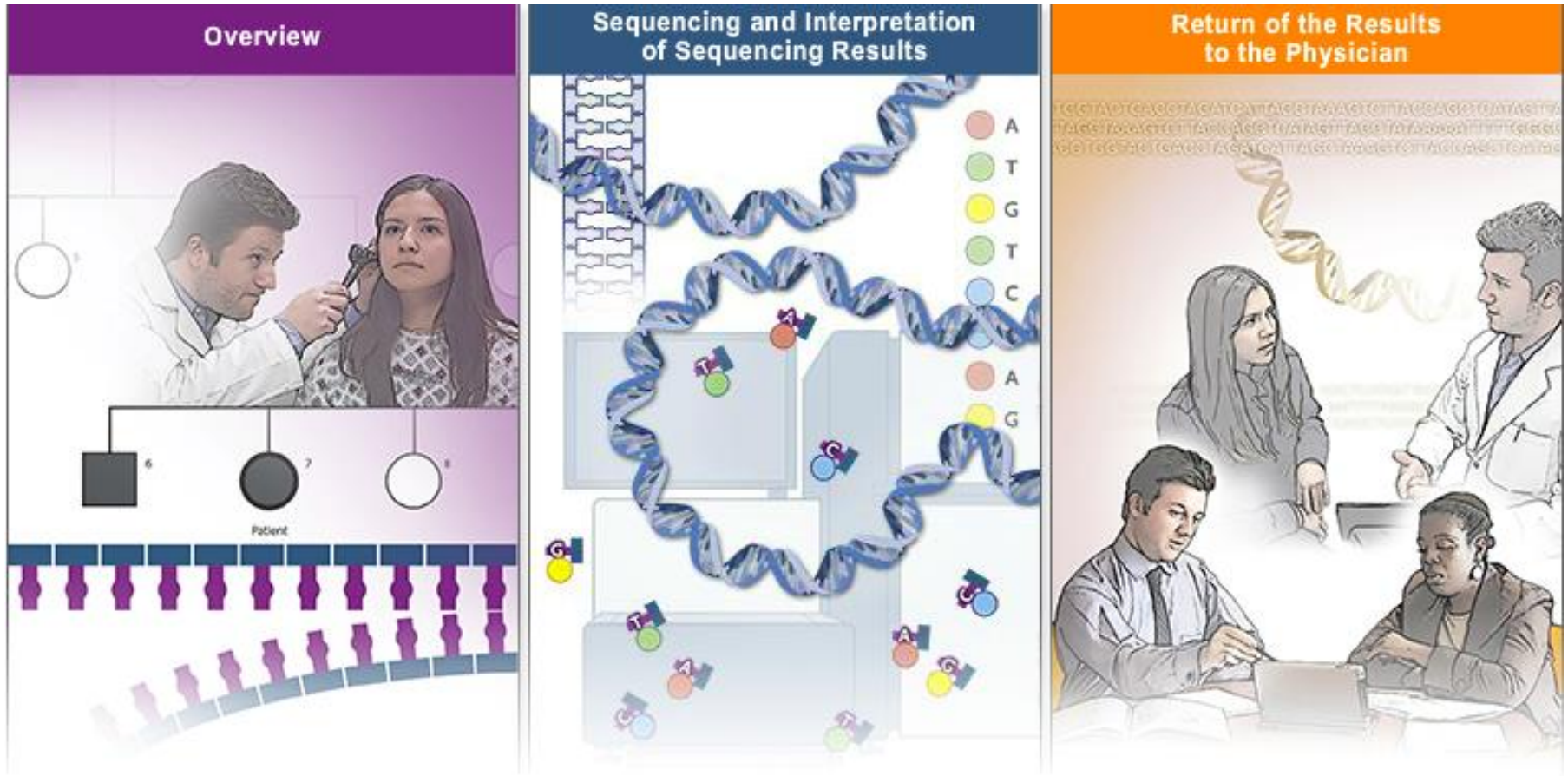
DISADVANTAGES:

- Reduced sensitivity in detecting CNV and other structural variants, (unless using optimized conditions).
- Difficulties in interpreting lot of variants of “uncertain pathogenic significance” detected.



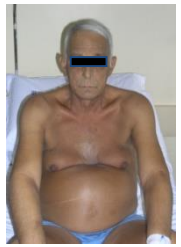
Lu JT, N Engl J Med 2014

Close relationships between clinicians, bioinformaticians, and geneticists needed



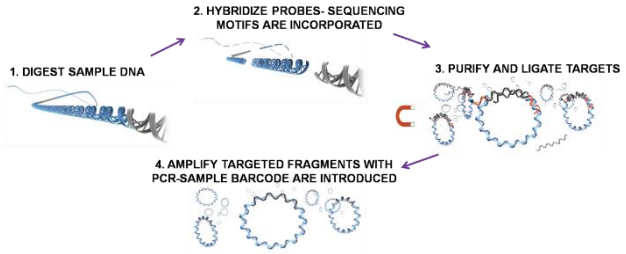
NEJM 2014

NGS panel for rare genetic iron disorders: our experience



Pts. selection

Halo-Plex™ PCR Technology
For Target Capturing



Illumina MiSeqDx™

	Iron metabolism Genetic Disorders	Genes Included in the panel	
		DISEASE-CAUSING GENES	Other genes (modulators?)
Iron Overload	*HFE HH*	HFE (and upstream region)	ACO1, ARNTL (intron), B2M, BMP4, BMP2, BMP6, BMPR1A, BMPR1B, BMPR2, CBRD1 (and upstream region), CREB3,EGLN1, EGLN3, EPAS1, EPOR, EPO, EPOR, FADS2, FAM132B, FLVCR1, FURIN (and upstream region), GDF2, GDF15 (and upstream region), GNPAT,HEPH, HIF1A, HP, IL1A, IL6, IL6R, IREB2, LCN2, NCOA4, NEO1, PCSK7 (and upstream regions), RGMA, RGMB, SCARA5, SERPINA1, SMAD1, SMAD4, SMAD5, SMAD9, STEAP3, STAT3, TFRC, TWSG1, VHL
	NON-HFE HH	SLC40A1, TFR2, HFE2, HAMP (and upstream region), BMP6	
	Aceruloplasminemia	CP	
	Atransferrinemia	TF	
	DMT1-Related iron disorders	SCL11A2	
	Autosomal Dominant Iron Overload	FTH1 (and upstream region)	
	Sideroblastic Anemia	ALAS2	
	Congenital dyserythropoietic anemia type II	SEC23B	
No Iron Overload	*Genetic Hyperferritinemia*	FTL (and upstream region)	
	Genetic Hyperferritinemia cataract		
Iron Deficiency	*IRIDA*	TMPRSS6	

Diagnosing non-classical HH by NGS panel in selected pts

Identification of novel mutations in hemochromatosis genes by targeted next generation sequencing in Italian patients with unexplained iron overload

Pt. ID	Age/sex	1stlevel genetic test	TS, Ferritin	LIC[a] (MR)	Liver biopsy	NGS	
#01	70/M	Wild-type[b]	80%, 1,450 µg l^{-1}	–	no (iron removed >10 g)	–	unexplained
#02	39/M	H63D +/–	61%, >1,000 µg l^{-1}	–	yes (HH "pre-cirrhotic")	HFE W163X +/–	Non classical HFE-HH
#03	48/M	H63D +/–	73%, >1,000 µg l^{-1}	300	No	HAMP R59X +/–	Digenic inheritance (HFE/HAMP)
#04	62/F	Wild-type[b]	60%, 1,786 µg l^{-1}	270	yes (siderosis 3+, periportal gradient)	–	unexplained
#05	58/M	H63D +/+	n.a., 1,089 µg l^{-1}	160	No	TFR2 D555N +/–	TFR2-related HH
#06	35/F	Wild-type[b]	100%, n.a.	–	yes (HH "pre-cirrhotic")	TFR2 N241I +/+	TFR2-related HH
#07	66/M	Wild-type[b]	48%, 2,352 µg l^{-1}	250	yes (siderosis 2–3+, periportal gradient)	–	unexplained
#08[c]	47/M	H63D +/–	95%, 6,242 µg l^{-1}	–	no (iron removed >10 g)	SLC40A1 A69T +/–	Ferroportin Disease

Molecular diagnosis

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Badar S, Am J Hematol 2016

Are there any “missing hemochromatosis gene(s)”?

NGS applications in selected pts. with “unexplained” HH:
Some cases remain unexplained!

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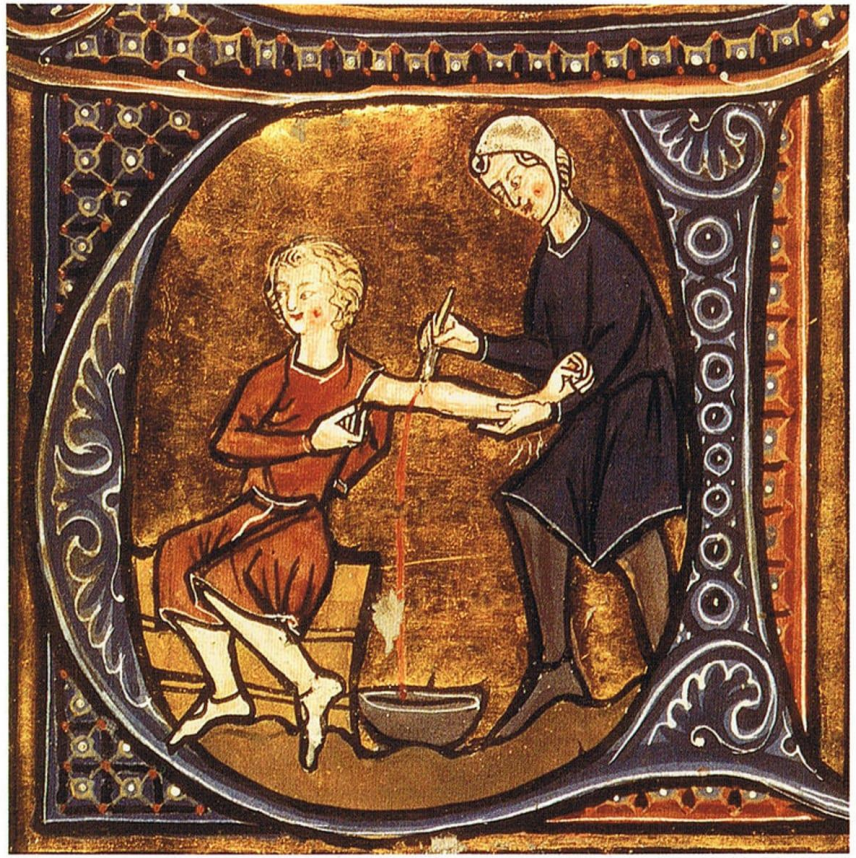
Therapeutic options



Phlebotomies well tolerated

Anemia typically absent in H., unless advanced disease (e.g. portal hypertension with hypersplenism/variceal bleeding) or comorbidities.

1

Phlebotomy induction phase

350-500 mL (according to sex/weight) every 1-2 weeks.

Check Hb (discontinue/delay if <11-12 g/dL) and serum ferritin (SF) every 4 phlebotomies. Goal: SF ~ 50-100 μg/L.

2

Phlebotomy maintenance phase

A phlebotomy every 2-3 to 4-6 months to keep SF within the desired range.

Lifelong (reduce or suspend after 70-75 years)

3

Erythrocytapheresis

Quick and safe, not universally available. Good option in pts. with **severe cardiomyopathy/liver disease** (isovolemic procedure).

4

Iron chelators

Only if phlebotomies contraindicated/unfeasible, or **in combination with phlebotomies in most severe cases**. DFO s.c. 25-40 mg/kg 5-7 days/week. Oral chelators can be used but off-label.

?

Hepcidin agonists

Intensive phlebotomies until iron deficiency may exacerbate hepcidin deficiency. Hepcidin agonist may be of some help in the future.

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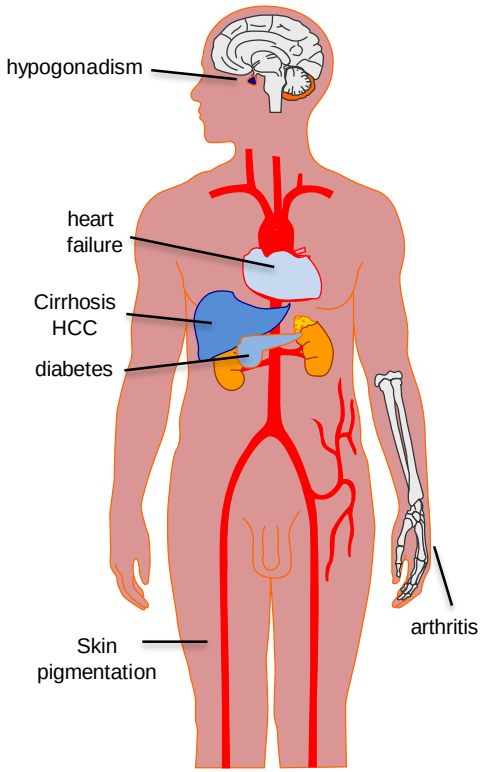
Personalized treatment in challenging patients



- **ADVANCED DISEASE**
- **HF WITH HEMODYNAMIC INSTABILITY**
- **ANEMIA**
  (GI bleeding, hypersplenism)
- **COMORBIDITIES**
  (e.g. renal failure, others)

- **ERYTHROCITAPHERESIS**
- **“LOW INTENSITY” PHLEBOTOMIES**
  (e.g. 150-200 ml at close intervals)
- **IRON CHELATORS**
  (alone or in combination with above)
- **HORMONE REPLACEMENT Thx.**
  e.g. insulin, androgens)
- **MISCELLANEOUS**
  e.g. bisphosphonates, anti-arthritis)

CONCLUSIONS – TAKE-HOME MESSAGES

1. **DIAGNOSIS OF RARE FORMS OF H. IS ESSENTIALLY CLINICAL**

(based on: ↑ SF and TSAT, clinical/imaging/pathological evidence of IO with no alternative explanation)

2. **MOLECULAR DIAGNOSIS USEFUL BUT NOT REQUIRED FOR TREATMENT**

(*e.g. for cascade screening in relatives; consultation with a referral center recommended)

3. **TREATMENT SIMILAR TO CLASSIC H.**

(personalized in advanced disease or challenging cases)

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