Approach to a high ferritin level: the hepatologist's perspective

Amer El-Sayed, M.D.

Hepatology day, LSGE

May 28, 2011

FERRITIN

- Major storage protein for iron
- Present in large amounts in macrophages and hepatocytes (storage)
- In erythroblasts (for metabolic purposes)
- Small concentrations in plasma (not transport protein like transferrin) → reflects total iron body stores
- Most widely used surrogate for iron overload (highly sensitive in Hemochromatosis), low specificity.

HYPERFERRITINEMIA: etiology

- Increased ferritin synthesis

  Acquired or genetic conditions, with or without iron overload

- Increased ferritin release

  From damaged cells: steatosis, steatohepatitis, chronic viral hepatitis, liver necrosis, acute hepatitis, acute MI, splenic infarct

- Clue: clinical setting

HYPERFERRITINEMIA: etiology

Iron overload

- Primary:
  - Hereditary hemochromatosis
  - Hereditary aceruloplasminemia
- Secondary:
  - Transfusion overload
  - Excess dietary iron
  - Porphyria cutanea tarda
    - Cutaneous photosensitivity
    - Hepatic iron overload
    - ↗ Urinary and fecal porphyrin excretion
  - Ineffective erythropoeisis (sideroblastic anemia)

Liver diseases / Acute inflammation

- NASH / NAFLD
- Viral hepatitis
- Familial hyperferritinemia-Cataract syndrome

Alcohol excess

- Regular consumption: disruption of normal iron metabolism
- ➔ Excess deposition of iron in liver in 1/3 of alcoholic patients
- Process: unclear. Both ferritin + transferrin involved.

Adams PC, J Hepatol, Feb. 2011

HYPERFERRITINEMIA

- > 90 % of outpatients:
  - Chronic alcohol intake
  - Inflammation (✓ CRP)
  - Cell necrosis (✓ TA- CK)
  - Malignancy (✓ ESR, imaging)
  - NAFLD and/or
  - Metabolic syndrome (✓HTN, BMI, Chol, TGL, Glucose)
- Often measured if:
  - Persistent elevation despite treatment
  - investigate fatigue, possible liver disease, anemia or neoplasia.

Reference concentration of ferritin

- Variable (lab, personal)
- Large multi-ethnic multi-racial screening study of iron overload north americans patients:

  > 300 μg/L in males

  > 200 μg/L in females
- Mean SF - % of patients with high SF
  - Higher in blacks, asians, pacific islanders vs. whites
- Transferrin
  - TS > 50 %
  - TS higher in asians, lower in african americans

  ⇒Elevated SF and TS are not always indicators of disease

Never test Ferritin/TS in acutely ill patients:
- Ferritin misleadingly high
- TS conversely low, may mask iron overload

Adams PC, NEJM 2005:352:1769-1778

Use of Transferrin saturation to interpret serum ferritin

- Clinicians rely on TS to interpret elevated ferritin levels:
  - Iron overload
  - Iron deficiency
  - Subnormal iron mobilization for erythropoeisis
- Reliability not 100% accurate
- Large population screening cohort → significant biological variability in serum TS

Use of Transferrin saturation to interpret serum ferritin

- 64230 patients
  - Non-fasting TS >45 % (males) and >50% (females)

    Se 75% **Sp 95%** in detection of C282Y homozygotes

    (fasting failed to increase sensitivity)
- ↓ reliability and specificity of TS in clarifying significance of high ferritin levels
- Acute infection / Menses / recent blood donation may decrease TS temporarily in patients with hepatic iron overload.

Adams PC, Am J Med 2007;120:e1-e7

Relationship between TS and liver iron concentrations

- TS predicts hepatic iron overload better in C282Y homozygotes.
- Some patients with normal TS and high ferritin may have hepatic iron overload (proven by histology)

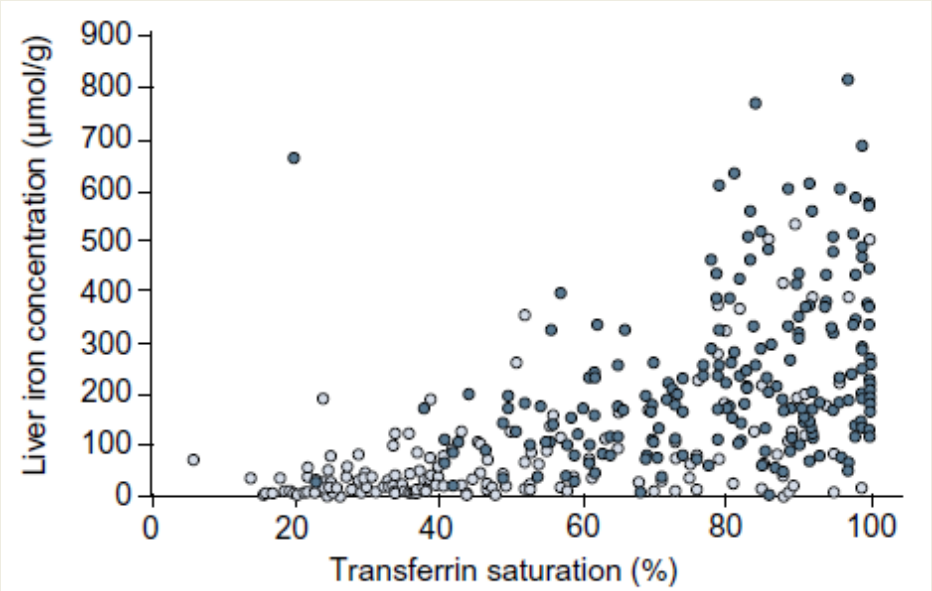
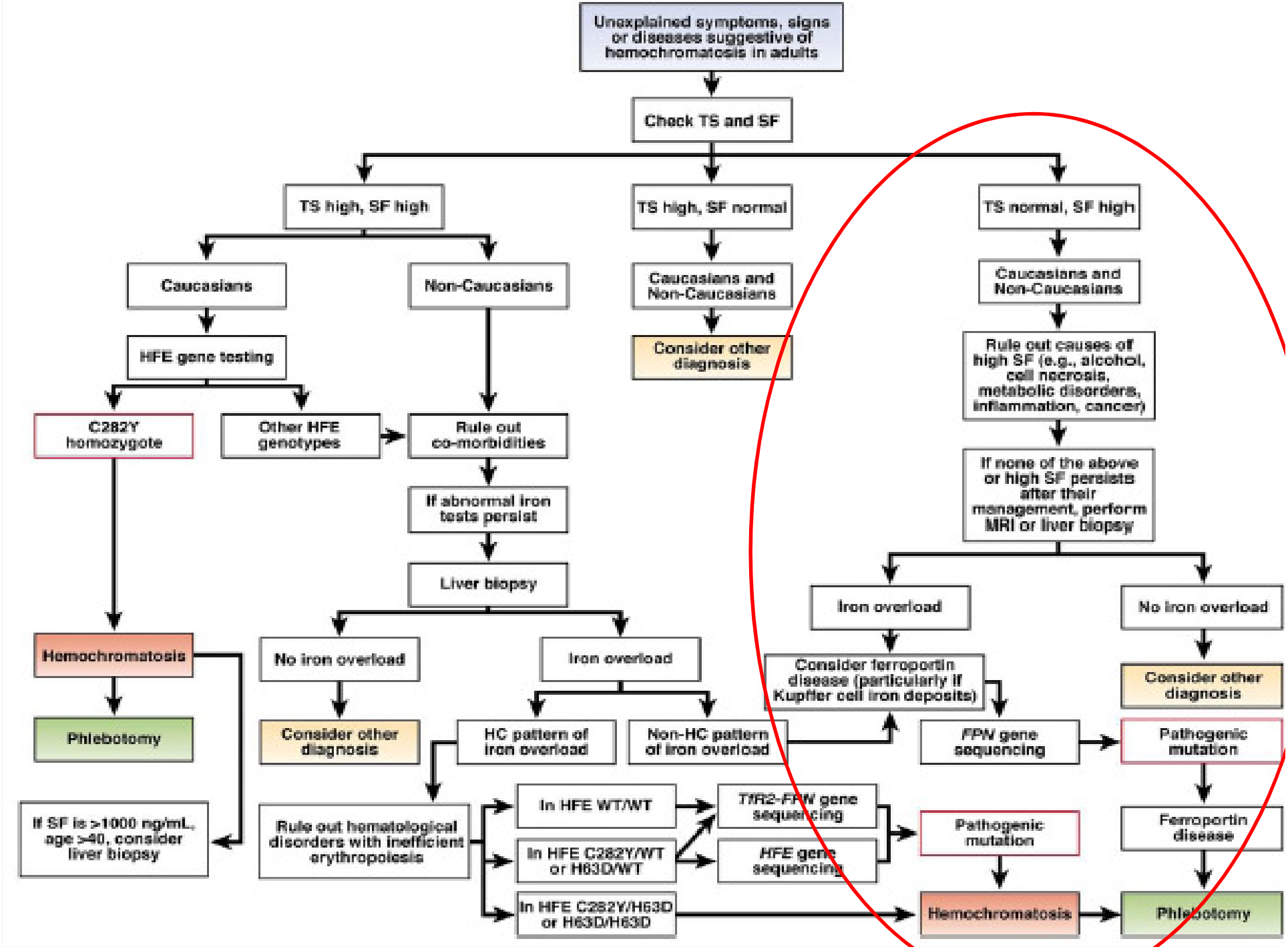


Fig. 1. The relationship between transferrin saturation and hepatic iron overload in C282Y homozygotes (●) and non-homozygotes (○).

Beaton M, Liver Int 2011;31:272-3.

TS for iron overload	Sensitivity (%)	Specificity (%)
>55%* (n = 371)	81	73
>50% (n = 371)	85	69
>45 (n = 371)	89	61
>55% in C282Y homozygotes (n = 209)	92	40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HFE gene testing
Consider other diagnosis
Rule out causes of high SF (e.g., alcohol, cell necrosis, metabolic disorders, inflammation, cancer)
C282Y homozygote
Other HFE genotypes
Rule out co-morbidities
If none of the above or high SF persists after their management, perform MRI or liver biopsy
If abnormal iron tests persist
Liver biopsy
Iron overload
No iron overload
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Consider ferroportin disease (particularly if Kupffer cell iron deposits)
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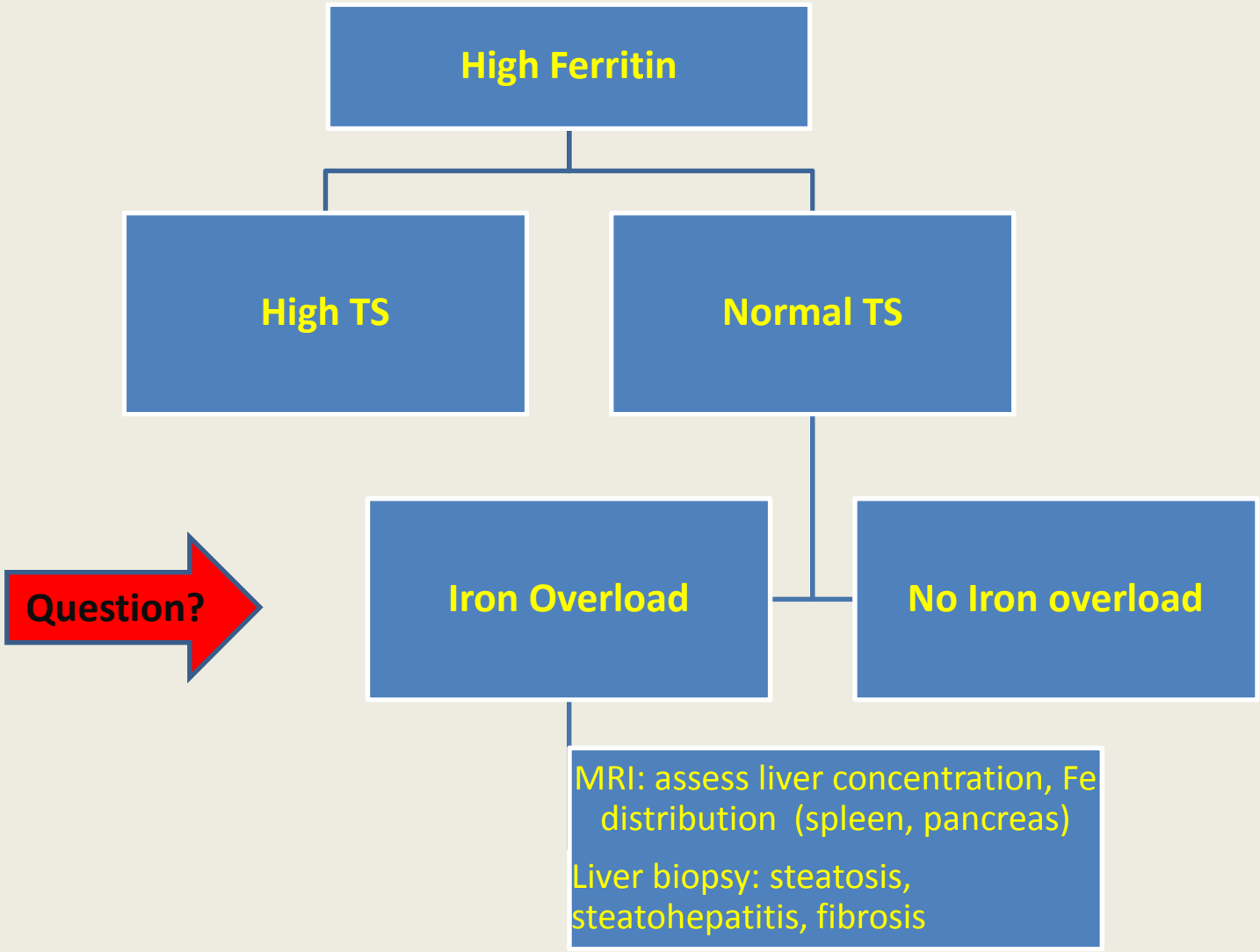

High Ferritin
High TS
Normal TS
Question?
Iron Overload
No Iron overload
MRI: assess liver concentration, Fe distribution (spleen, pancreas)
Liver biopsy: steatosis, steatohepatitis, fibrosis

High ferritin, normal TS

Useful to measure

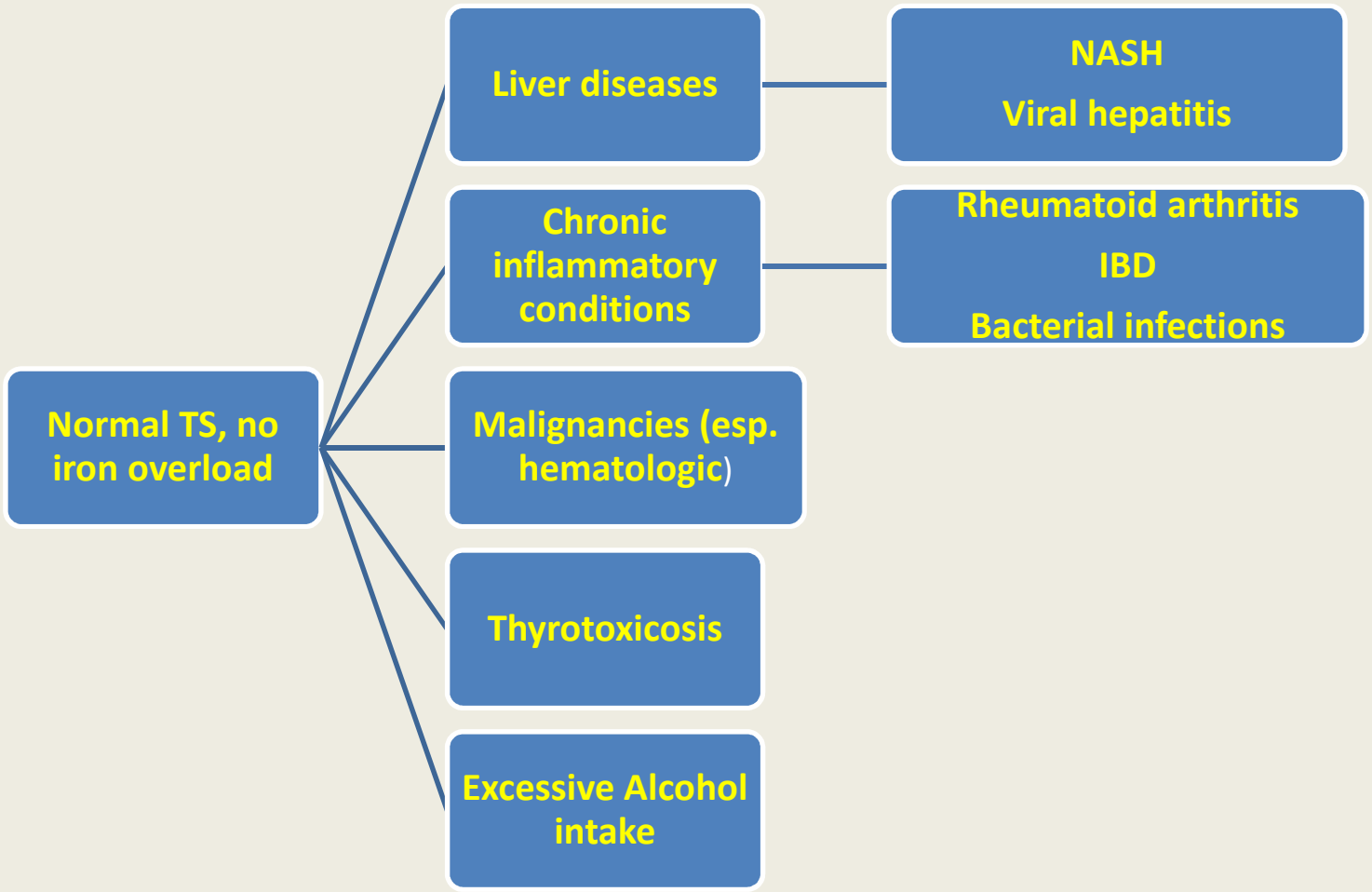
AST, ALT → hepatocyte necrosis
iron overload

U/S liver → fatty liver, steatohepatitis

Alcohol consumption → history, GGT

HBsAg, HCV Ab → ↑ ferritin without Fe overload

Common causes



Normal TS, no iron overload

HEREDITARY HYPERFERRITINEMIA-CATARACT SYNDROME

- Up-regulation of L-Ferritin
- Constantly elevated ferritin levels
- No iron overload
- L-ferritin deposition in ocular lens causing bilateral cataract at early age

Hetet G, Blood 2003;102:1904-1910

DYSMETABOLIC SYNDROME

- Metabolic syndrome:
  - Obesity, Dyslipidemia
  - Diabetes, Hypertension
- Liver biopsy: Iron deposition in Kupfer cells (peri-portal-hepatocytic in HFE-HC) / steatosis
- No iron overload

Normal TS, hepatic iron overload

ACERULOPLASMINEMIA

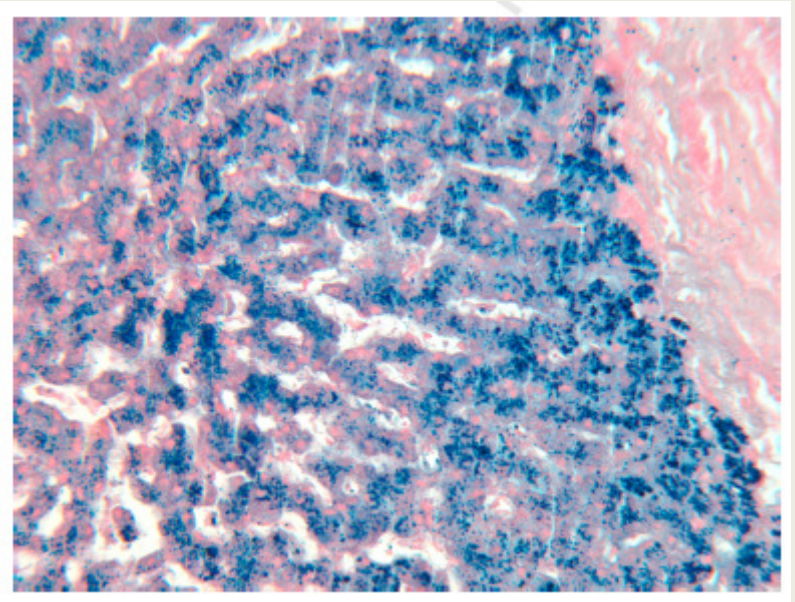
- Rare genetic syndrome
- Mutation in gene that encodes for ceruloplasmin
- Retinal abnormalities
- Neurologic manifestations (dementia, cerebellar ataxia)
- Vs. Wilson's:
  - Absence of ceruloplasmin in serum
  - Absence of excess copper storage in liver
  - Absence of excess Ucopper

FERROPORTIN DISEASE

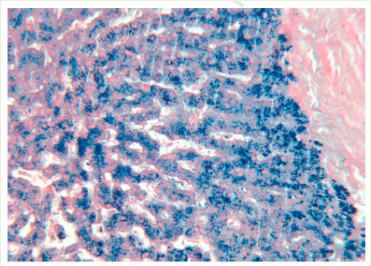
- Mutation of SLC40A1 encoding for ferroportin
- Rare, autosomal dominant
- Significant liver iron deposition

Liver biopsy

- Well established tool for evaluation of iron overload + concomittant liver diseases
- In normal TS patients, indication to biopsy:
  - High SF and presence of confounding factors
  - Exclude iron overload
  - Stage, diagnose liver disease
- Not routinely recommended to assess Fe overload if SF < 1000 µg/L



Liver biopsy in confirmed hepatic overload

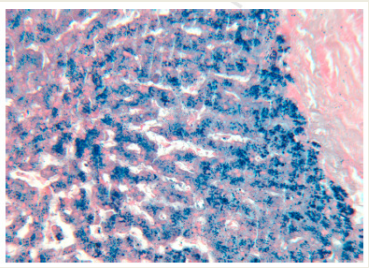


- Limited indication
- With availability of HFE-genotyping:
  - Homozygous C282Y + high iron body stores enough for diagnosis of HFE-HC
  - Histology only to grade degree of fibrosis
- In C282Y homozygous patients, if:
  - Normal liver/Ferritin < 1000 µg/L/normal AST

    ⇒**NPV ~ 95%** for significant liver fibrosis
- If 1, 2 or all criteria not met ➔High risk of fibrosis

Guyader et al, Gastroenterol 1998;115:929-936.

Fibrosis regression: role for liver biopsy

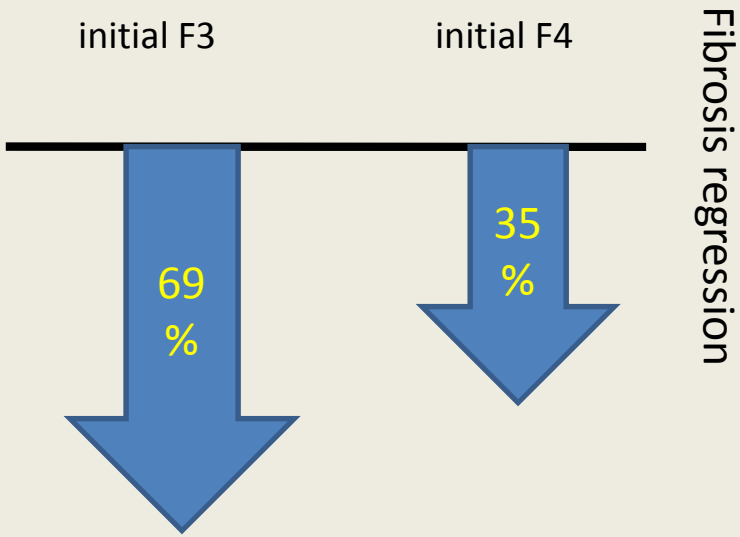


- 36 C282Y homozygous patients
- Severe fibrosis: bridging fibrosis to cirrhosis
- Regression noted in 69% of F3 vs. 35% of F4

Falize J, Hepatology 2006;44:472-477

- Improvement / resolution of esophageal varices reported with phlebotomy

Francanzani AL, Hepatology 1995;22:1127-1131



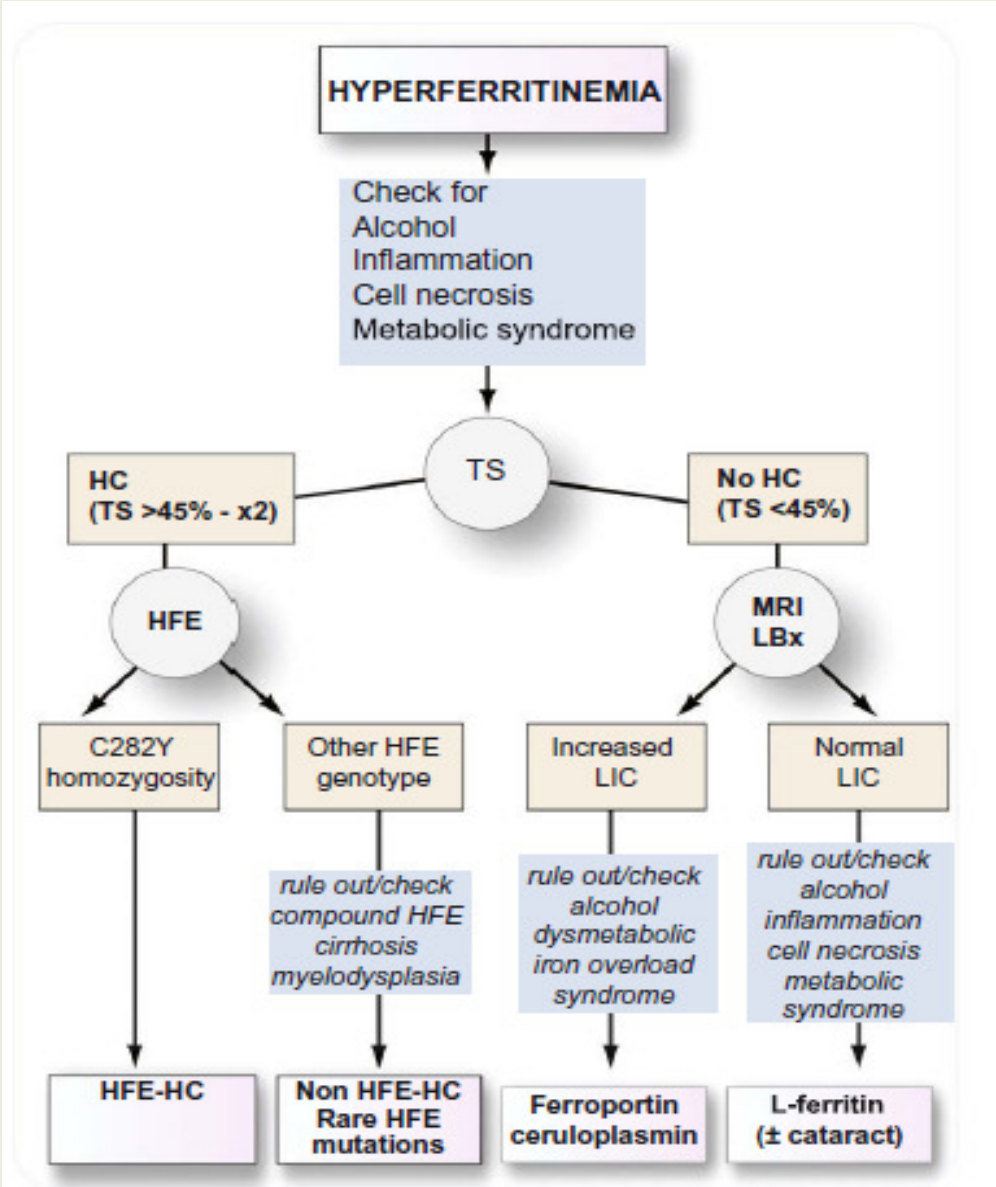
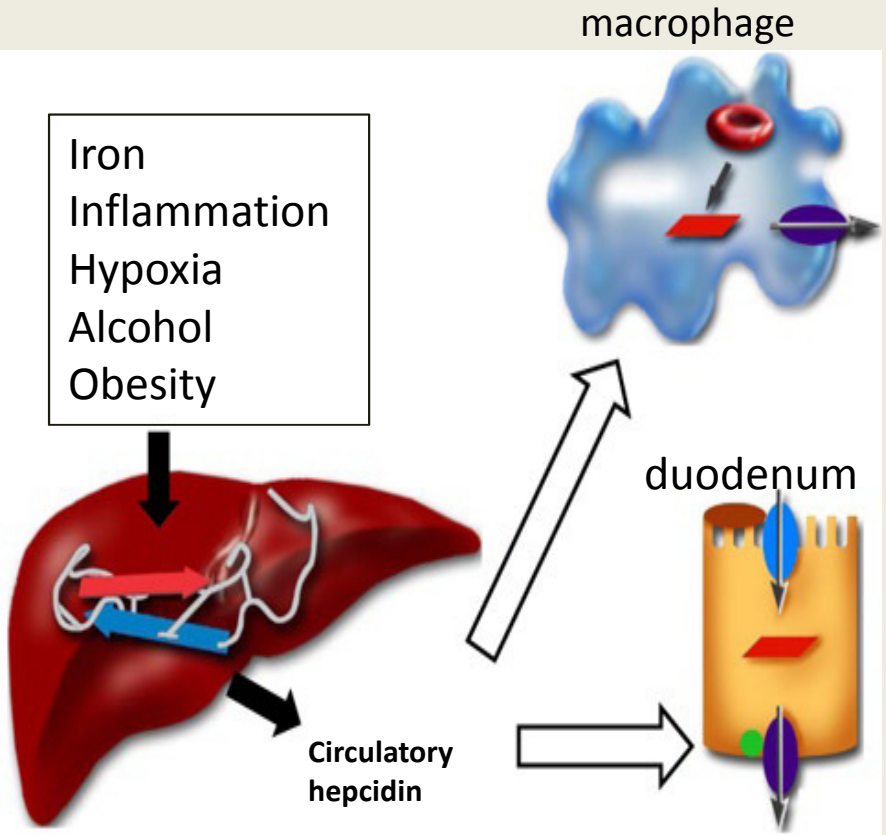


Fig. 3. Proposed algorithm for the diagnosis of genetic causes of hyperferritinemia.

Iron overload disorders
High ferritin, high TS

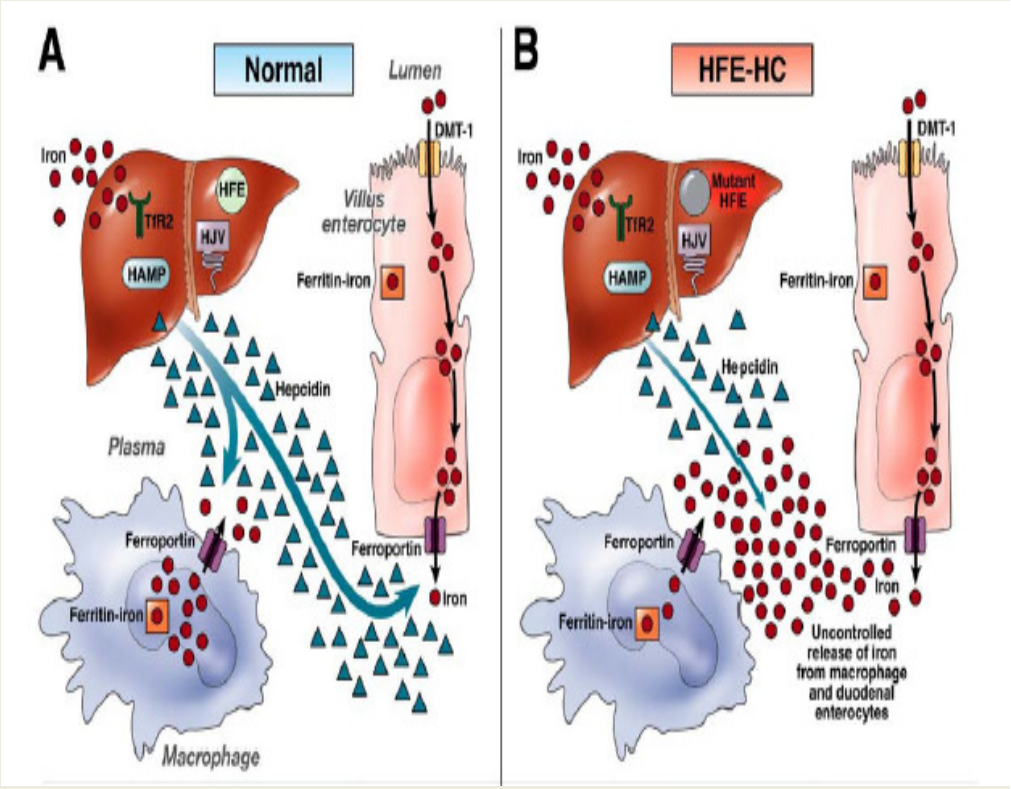
Iron metabolism

- Fe reutilized in closed circuit
- Central role of liver through hepcidin production
- Hepcidin: major regulator of intestinal iron and iron delivery to plasma
- Hepcidin controls iron transport into dodenum and iron export in macrophages
- Hepcidin degrades ferroportin (transport) ➔blocks Fe release from cells to plasma



Pathophysiology of iron overload disorders

- Hepcidin deficiency: central pathogenic factor in HC
- Unrestricted flow of iron into the plasma iron pool
- Some taken up by bone marrow, some stored in hepatocytes as ferritin



Genetic Iron overload disorders

HEMOCHROMATOTIC

- Normal erythropoeisis
- Parenchymal Fe distribution related to hepcidin dysfunction

HFE-HC (type 1)

JUVENILE HC (type 2)

Transferrin Rec 2 TFR2 (type 3)

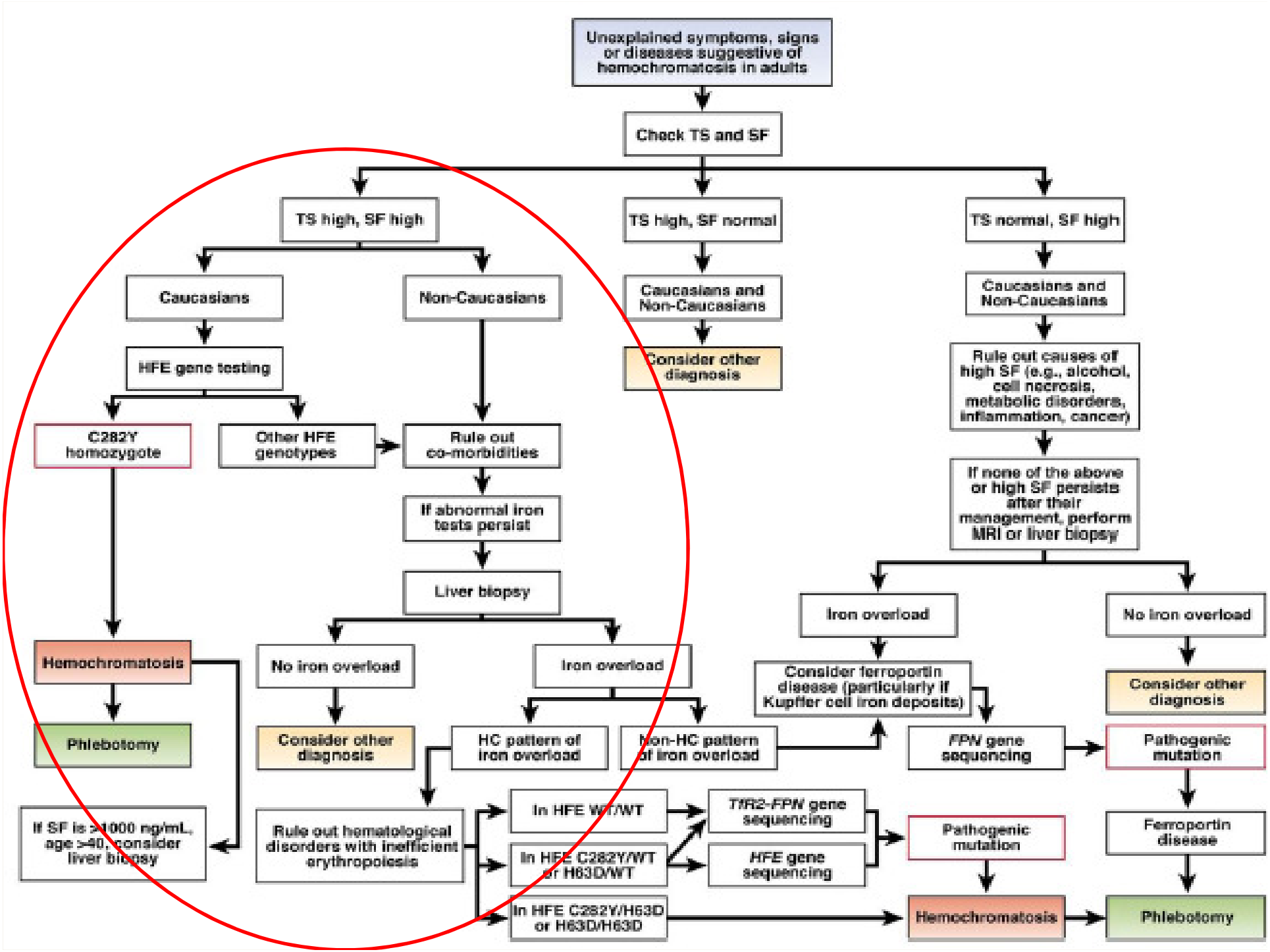
Type B ferroportin disease

NON-HEMOCHROMATOTIC

- Type A ferroportin disease
- Hereditary aceruloplasminemia
- Hereditary atransferrinemia

Acquired iron overload disorders

- Chronic excessive iron supply
- Hematologic disorders
  - Thalassemia
  - Myelodysplastic syndrome
  - Sickle cell anemia
- Chronic liver diseases
  - Destruction of hepatocytes
  - Decreased hepcidin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Recommendations for Genetic testing

EASL guidelines – J. hepatol 2010;53:3-22

- General population
  - Unexplained chronic liver disease with high TS
  - Pts with Porphyria CT, well-defined chondrocalcinosis, HCC
  - Type 1 DM
- Suspected iron overload: fasting SF and TS
  - HFE genotyping only if TS elevated (at least once)
  - Testing for C282Y and H63D polymorphism
- Consider liver biopsy if ferritin > 1000 µg/L

Ferritin: a prognostic marker

- SF: predictor of risk of cirrhosis
- Multiples studies:
  - Cirrhosis rarely occurs if ferritin < 1000 µg/L
- Allows estimation of incidence of cirrhosis in C282Y homozygous patients
  - Liver Bx in 350/672 pts (SF > 500 µg/L, hepatomegaly, elevated TA)
  - Cirrhosis: 5.6% of males, 1.9% of females (all ferritin > 1000 µg/L)
  - ROC curve Ferritin 1653 µg/L
    - Se 90%, Sp 92 % for predicting cirrhosis

Guyader D, Gastroenterol 1998; Morrison ED, Arch Int Med 2003, Powell M, Arch Int Med 2006

Ferritin: monitor of treatment

- SF sufficient to monitor iron depletion
- Endpoint of therapeutic phlebotomy (standard of practice)
  - SF < 20-50 μg/L, TS < 30 % (within 1-2 yrs)
- Maintenance (prevent re-accumulation)
  - Keep SF between 50-100 μg/L
- Other approach
  - Resume phlebotomy when SF reaches upper limit of normal

Ferritin: predictor of steatosis in chronic liver diseases

- 124 patients with hyperferritinemia
- Steatosis confirmed by U/S (present or absent)
- Histology in 53 pts only
- 43% hep C, 46% NAFLD/NASH, 11% AFLD
- Ferritin: independent predictor of steatosis (in non-obese non alcoholic patients)
- High SF associated with more advanced disease (low platelets, portal hypertension)

Radicheva M. Trakia J Sci 2010

Ferritin and OLT

- Hypothesis: elevated SF important predictor of mortality in patients awaiting OLT, independently of MELD
- Retrospective analysis
- 191 patients with cirrhosis
- 2000-2006

Walker N. Hepatology 2010

- SF important and independent factor in predicting 180 d and 1 year mortality

-Identified both in study and validation cohort

-Higher frequency of liver related complications during follow-up in patients with high SF (necro-inflammatory activity)

Table 3. Variables Associated with 180 day Waiting List Mortality in the (A) Study Population and (B)Validation Population

	Univariate Analysis		Multivariate Analysis	
Variable	HR [CI]	*P* Value	HR [CI]	*P* Value
	(A) Study Population			
Age	1.01 [0.96-1.06]	0.67		
Male sex	1.61 [0.54-4.80]	0.39		
MELD	1.09 [1.02-1.17]	0.017	1.03 [0.95-1.13]	0.46
Presence of HCC	1.72 [0.66-4.45]	0.27		
SF <200 μg/L	1.00	-		
SF 200-400 μg/L	5.35 [1.38-20.81]	0.015	4.62 [1.17-18.2]	0.03
SF >400 μg/L	5.68 [1.58-20.39]	0.008	3.54 [0.91-13.82]	0.07
Serum sodium	0.88 [0.82-0.94]	<0.001	0.89 [0.83-0.96]	0.002
	(B) Validation Population			
Age	1.003 [0.96-1.05]	0.90		
Male sex	0.81 [0.33-1.97]	0.64		
MELD	1.15 [1.10-1.21]	<0.0001	1.19 [1.12-1.26]	0.0001
Presence of HCC	0.43 [0.12-1.46]	0.17		
SF > 500 μg/L	8.07 [2.37-27.55]	0.0001	10.52 [2.88-38.4]	0.0001
Serum sodium				
< 126 mmol/L	4.80 [1.54-15.02]	0.007		
< 131 mmol/L	3.75 [1.46-9.62]	0.006		

Table 4. Variables Associated with 1-Year Waiting List Mortality in the (A) Study Population and (B) Validation Population

	Univariate Analysis		Multivariate Analysis	
Variable	HR [CI]	*P* Value	HR [CI]	*P* Value
	(A) Study Population			
Age	1.02 [0.98-1.07]	0.33		
Male sex	2.01 [0.69-5.86]	0.20		
MELD	1.10 [1.03-1.18]	0.006	1.04 [0.96-1.13]	0.30
Presence of HCC	1.45 [0.58-3.66]	0.43		
SF <200 μg/L	1.00	-		
SF 200-400 μg/L	5.16 [1.54-17.28]	0.008	4.69 [1.38-15.95]	0.01
SF >400 μg/L	5.32 [1.73-16.36]	0.004	3.49 [1.06-11.49]	0.04
Serum sodium	0.88 [0.82-0.94]	<0.001	0.90 [0.84-0.96]	0.002
	(B) Validation Population			
Age	1.02 [0.97-1.07]	0.47		
Male sex	0.74 [0.34-1.60]	0.45		
MELD	1.15 [1.10-1.21]	0.0001	1.2 [1.12-1.27]	0.0001
Presence of HCC	0.58 [0.22-1.53]	0.27		
SF > 500 μg/L	11.05 [3.33-36.7]	0.0001	14.3 [4.10-50.47]	0.0001
Serum sodium				
< 126 mmol/L	4.80 [1.54-15.20]	0.007		
< 131 mmol/L	2.8 [1.16- 6.8]	0.02		

AUC for MELD vs. MELD+SF

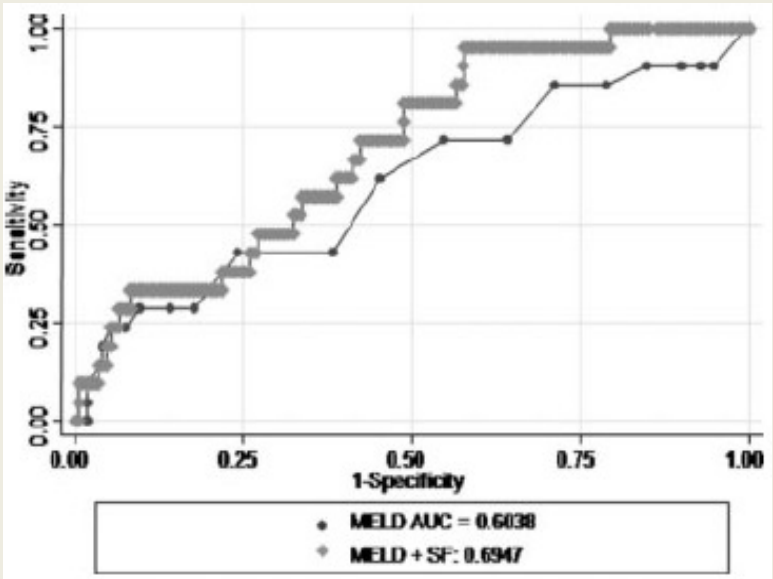


Fig. 2. ROC curve of MELD and MELD plus SF as predictors of mortality at 180 days.

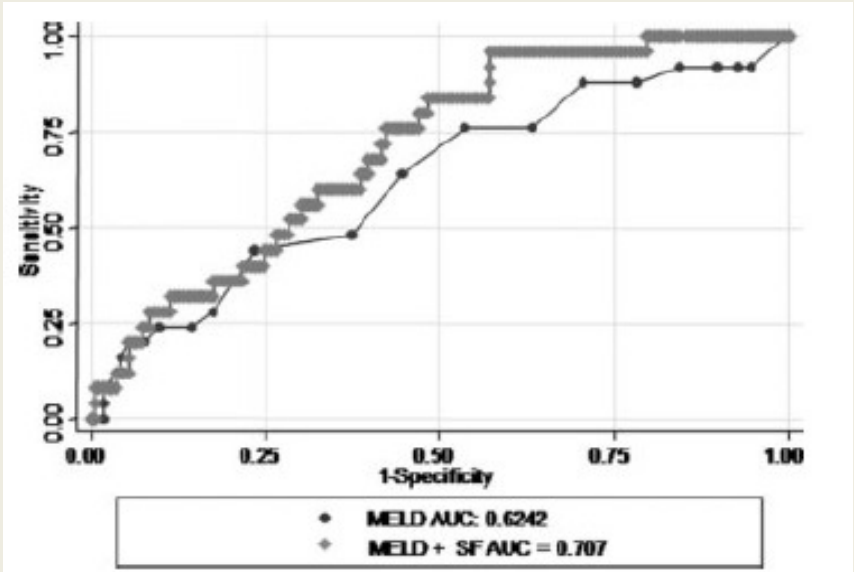
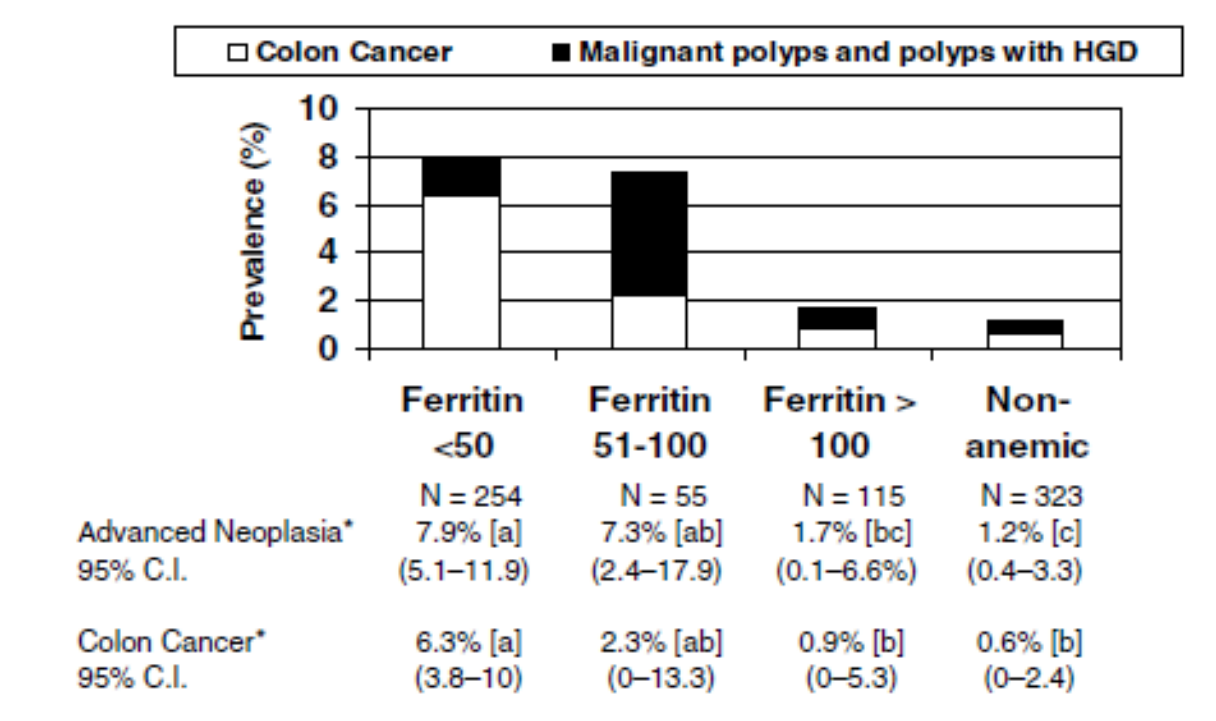


Fig. 3. ROC curve of MELD and MELD plus SF as predictors of mortality at 1 year.

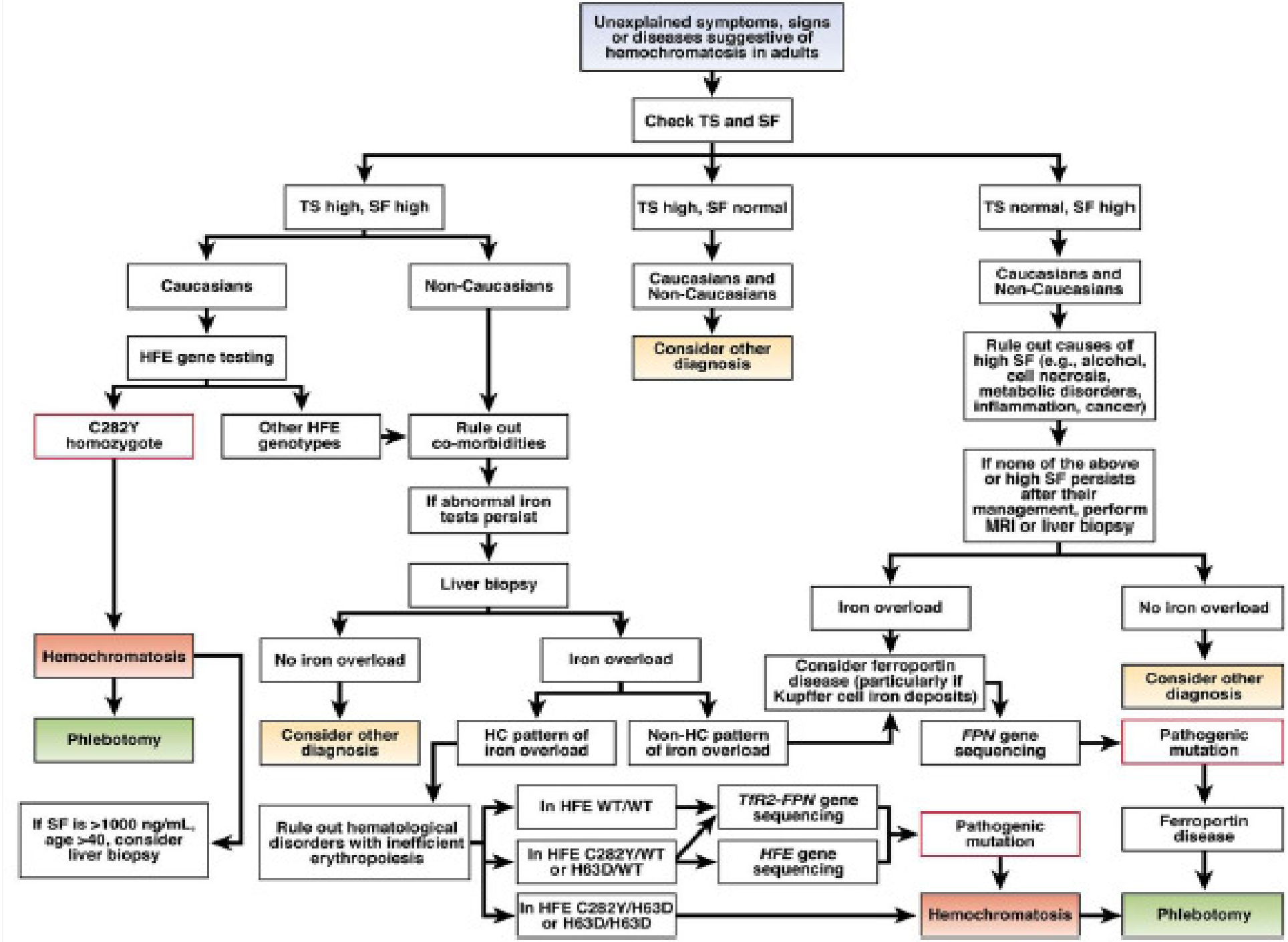
Ferritin in evaluation of anemia by colonoscopy



	Ferritin <50	Ferritin 51-100	Ferritin > 100	Non-anemic
	N = 254	N = 55	N = 115	N = 323
Advanced Neoplasia*	7.9% [a]	7.3% [ab]	1.7% [bc]	1.2% [c]
95% C.I.	(5.1–11.9)	(2.4–17.9)	(0.1–6.6%)	(0.4–3.3)
Colon Cancer*	6.3% [a]	2.3% [ab]	0.9% [b]	0.6% [b]
95% C.I.	(3.8–10)	(0–13.3)	(0–5.3)	(0–2.4)

Conclusion: Ferritin value of 100 µg/L should be used as cut-off for selecting patients with anemia for colonoscopy

Mandeep S. Am J Gastro 2007:102:82-88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