MAYO CLINIC

# Update in Hemochromatosis

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Division of GASTROENTEROLOGY & HEPATOLOGY

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## Disclosures

- No Disclosures
- No Financial Conflicts of Interest

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## Objectives

- Understand iron metabolism and pathophysiology of iron overload
- Review genetic mutations in hereditary hemochromatosis (HH) and their penetrance
- Review the typical laboratory findings and clinical manifestations of HH
- Discuss the management of patients with HH

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58 y/o asymptomatic man is referred for elevated serum iron studies obtained as part of an insurance physical. Iron = 210 μg/dl (normal 35-145); TS% = 80% (normal 14-50%); ferritin = 980 μg/L (normal 20-200). PMH unremarkable. He consumes 2-3 beers each day of the weekend and does not use iron supplements. He is adopted and family history is not available Exam is normal. Repeat TS is 74%. What would you recommend?

1. No further evaluation
2. *HFE* gene test
3. Therapeutic phlebotomy
4. MRI of the liver to look for iron deposition
5. *HFE* gene test and phlebotomy

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# Adult Inherited Liver Diseases

| | Hereditary Hemochromatosis | Wilson disease | A1AT deficiency |
|---|---|---|---|
| Inheritance | Recessive | Recessive | Co-dominant |
| Homozygote frequency | 1:250 | 1:30,000 | 1:2000 |
| Heterozygote frequency | 1:10 | 1:100 | 1:30 |
| Gene | HFE | ATP7B | "A1AT" |
| Number of mutations | 2 (C282Y, H63D) | >200 | ZZ |
| Chromosome | 6 | 13 | 14 |

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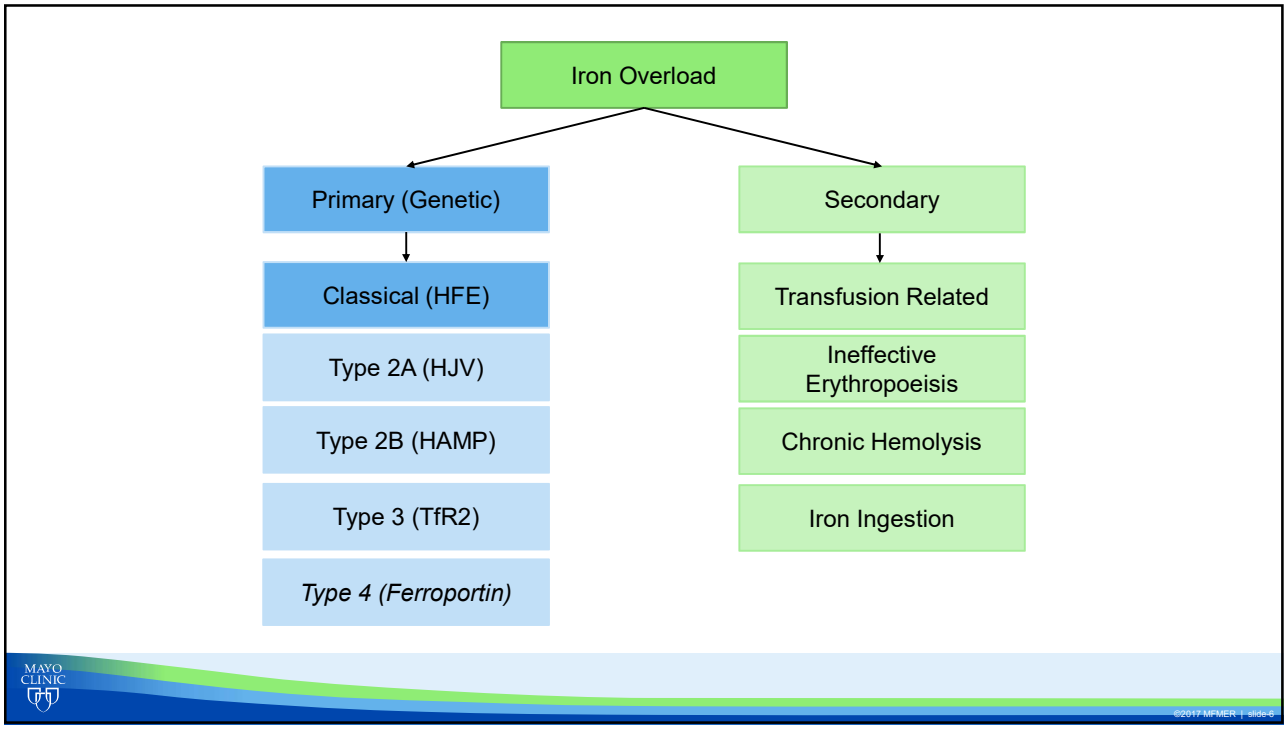


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## Hemochromatosis: Pathophysiology

- Loss of feedback inhibition leading to inappropriate iron absorption by enterocytes
- Hepatocytes regulates bioavailable iron through secretion of *hepcidin*
  - Hepcidin interacts with *ferroportin* transmembrane protein on enterocytes inhibiting release of iron from the basal membrane
- Mutant HFE fails to respond to adequate iron stores with failure to upregulate hepcidin (loss of feedback inhibition)

Radford-Smith DE, et al. *Int Med J* 2018;48:509-16
Kowdley KV, et al. *Hep Comm* 2021;5:723-25

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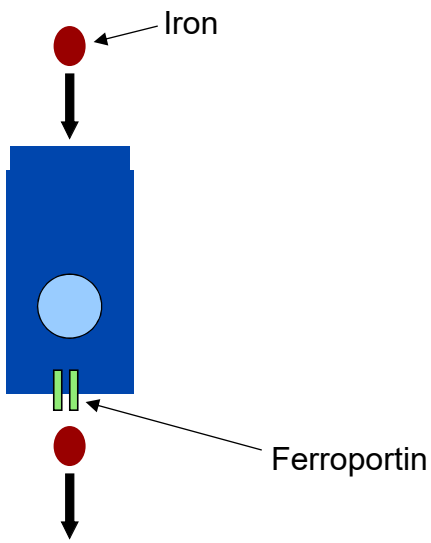


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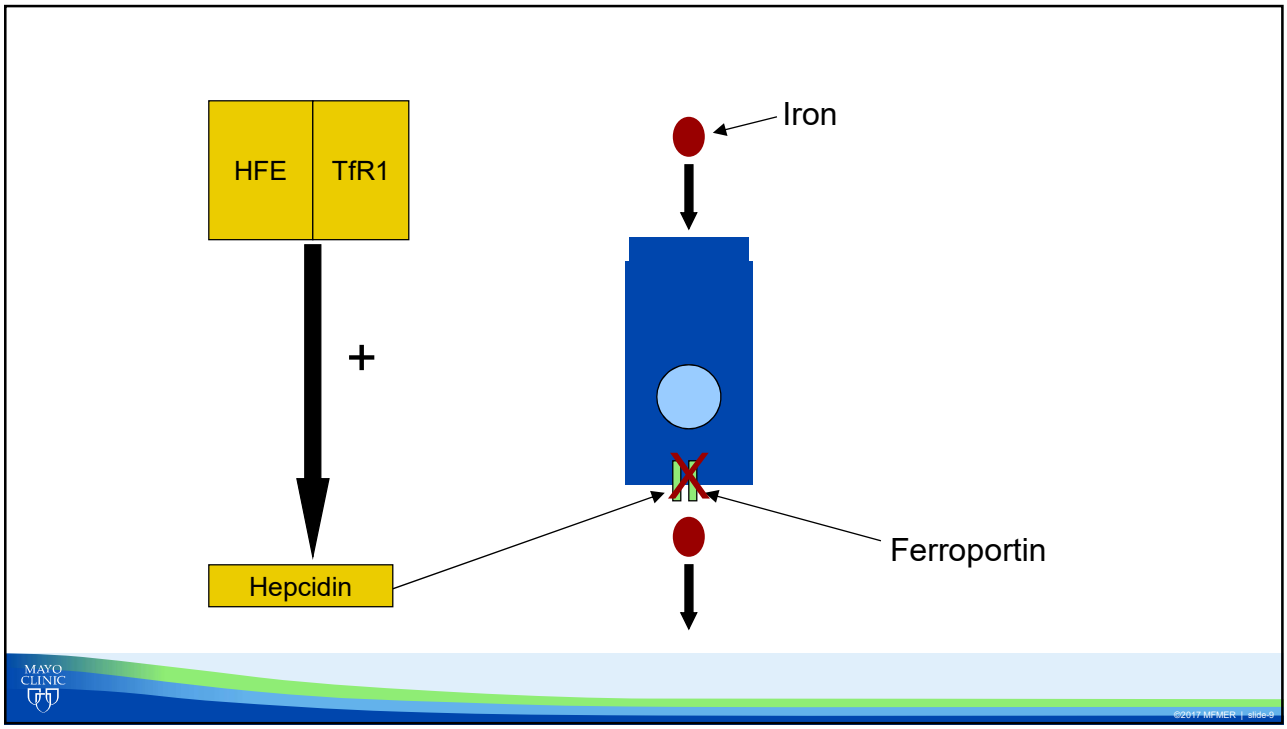
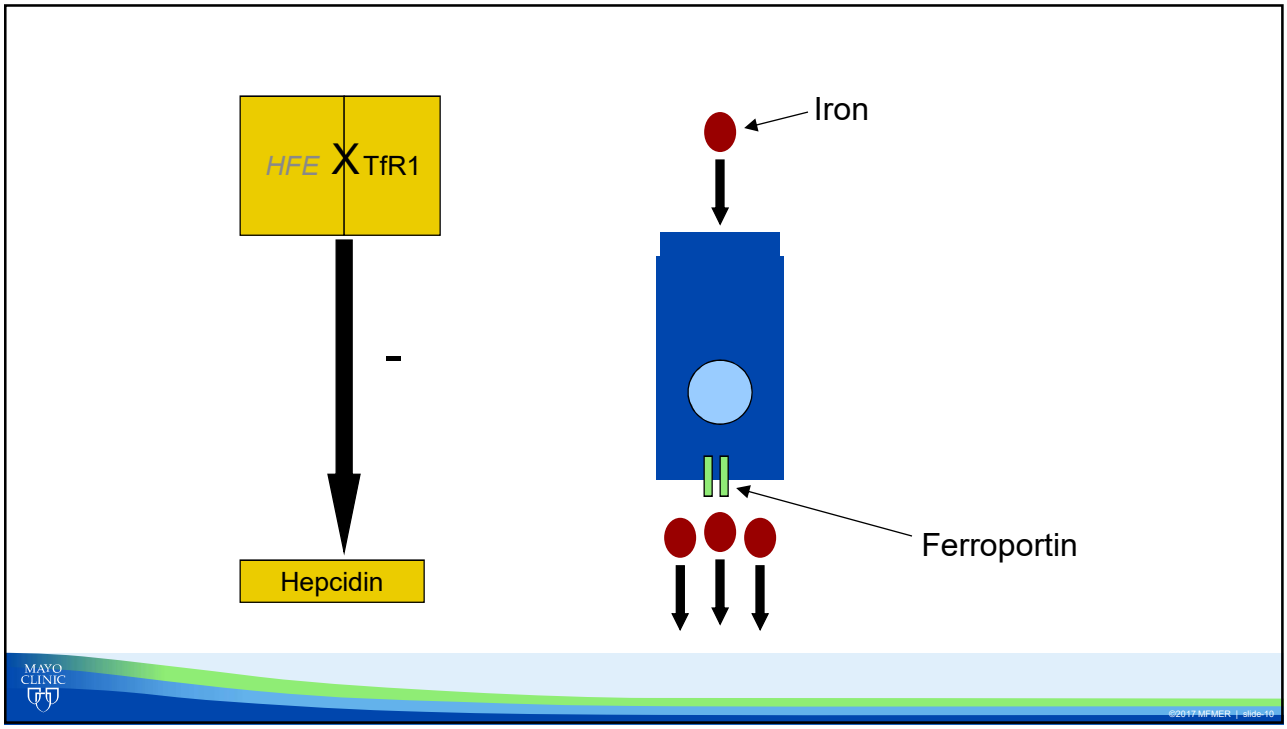

HFE
TfR1
+
Hepcidin
Iron
Ferroportin


HFE
TfR1
-
Hepcidin
Iron
Ferroportin

## Hemochromatosis: Gene Mutations

- Classical (Type 1) Hemochromatosis is associated with mutations in the *HFE* protein
  - Non-*HFE* mutations impact hepcidin or ferroportin
- Mendelian autosomal recessive inheritance pattern with variable penetrance
  - Except for ferroportin disease (Type 4) which has an autosomal dominant inheritance pattern
- HFE mutations C282Y and H63D (most commonly tested) account for approximately 85% of HH cases

Palmer WC, et al. *J Gen Intern Med* 2018;33(12):2230-6

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## Hemochromatosis: Penetrance

- *Genes are permissive for iron overload but are not the disease (genetics ≠ destiny)*
- C282Y/C282Y homozygote is the most common mutation associated with clinically evident iron overload (80% of cases)
  - Typical presentation is in 5$^{th}$ decade of life or later
  - 50-90% penetrance
  - Less/later in women due to reproductive blood loss
- Carrier state (C282Y/Wild Type) not associated with iron overload (but tend to have higher than average iron biomarkers)

Palmer WC, et al. *J Gen Intern Med* 2018;33(12):2230-6

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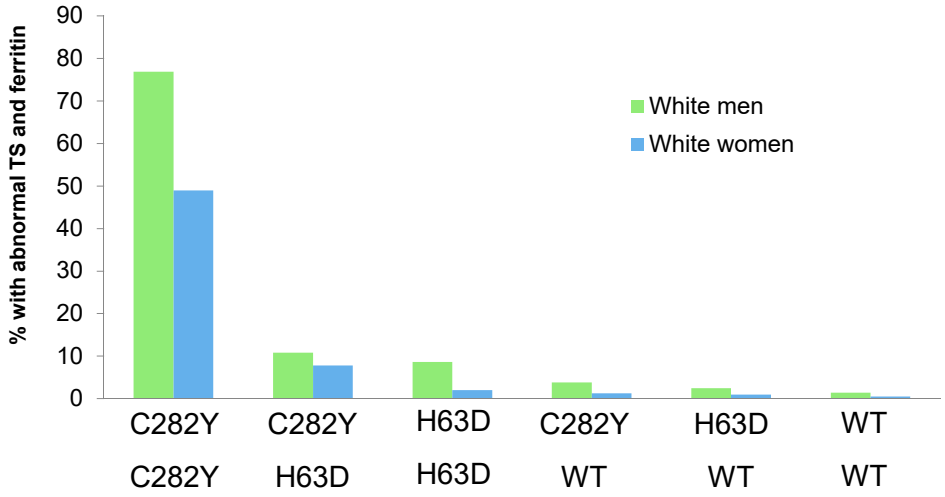
# Prevalence of Abnormal Iron Tests in Gene Tested Patients




Barton, et al; *Genetic Testing* 2005

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# Hemochromatosis: Diagnostic Testing

- Fasting Transferrin Saturation ≥ 45% AND elevated ferritin
  - Exclude secondary iron overload (hemolysis, etc).
  - Proceed with HFE gene-testing
- Liver biopsy in selected cases (to exclude other liver diseases or identify advanced fibrosis)
  - Abnormal ALT
  - Age > 40 AND Ferritin > 1000 mcg/mL
    - Cirrhosis rare in C282Y/C282Y with low ferritin and normal enzymes
  - Non-C282Y homozygote and diagnosis in doubt

*Modified from AASLD Practice Guidelines*

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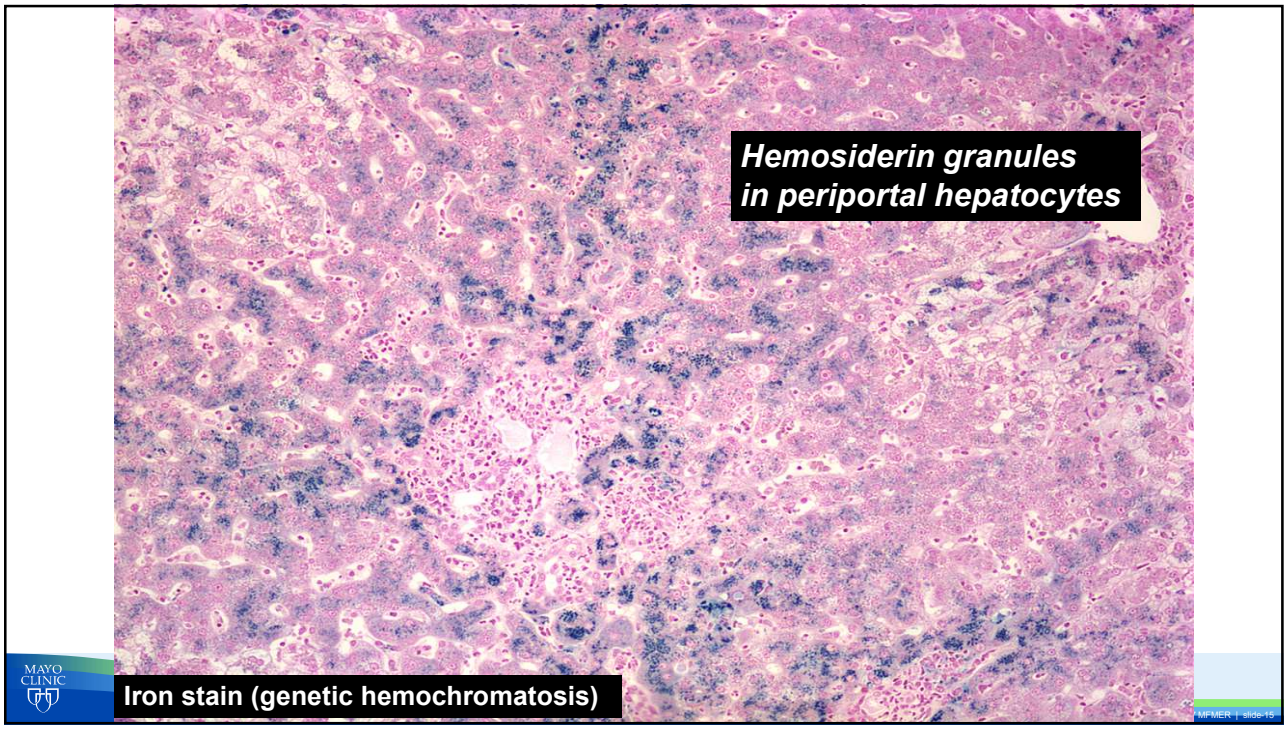
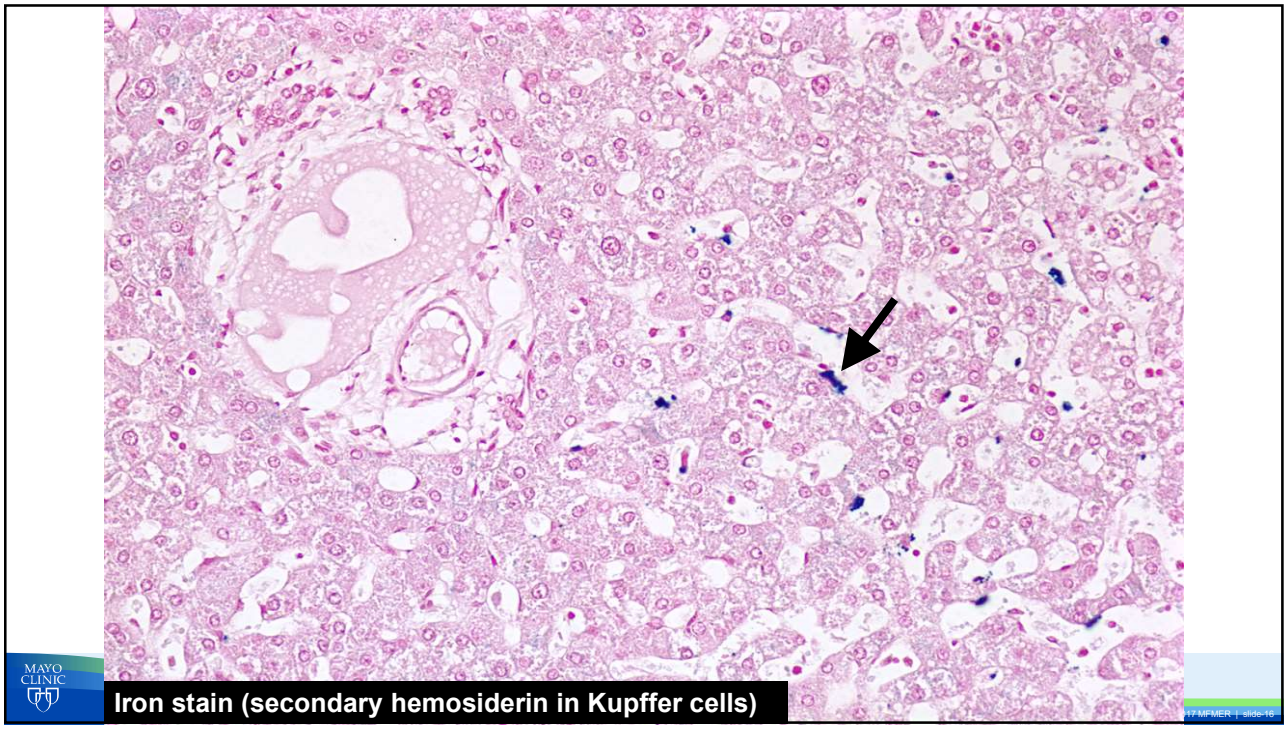

Hemosiderin granules
in periportal hepatocytes
Iron stain (genetic hemochromatosis)


Iron stain (secondary hemosiderin in Kupffer cells)

## Hemochromatosis: Systemic Manifestations

- Arthritis:
  - "Iron first" small joints of the hand – 2nd and 3rd metacarpals
  - Does not improve with iron depletion
- Cardiac: restrictive cardiomyopathy
  - Typical echo/cardiac MRI findings
- Endocrine:
  - Diabetes is sufficiently common as to often be misleading (DM2 with NASH and secondary hyperferritinemia as an acute phase reactant)
  - Hypogonadism (secondary to pituitary deposition)

Palmer WC, et al. *J Gen Intern Med* 2018;33(12):2230-6

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67 y/o asymptomatic woman is referred for abnormal liver tests obtained as part of her diabetes care. Screening for viral, autoimmune hepatitis are negative. Iron = 110 μg/dl (normal 35-145); ferritin = 490 μg/L (normal 20-200). PMH notable for obesity, DM2, HTN and dyslipidemia. FMH is positive for "fatty liver" in multiple siblings. No alcohol use. Exam is normal. What would you recommend?

1. No further evaluation
2. *HFE* gene test
3. Therapeutic phlebotomy
4. MRI of the liver to look for iron deposition
5. *HFE* gene test and phlebotomy

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## Hemochromatosis: Isolated Elevated Ferritin

- Isolated elevated ferritin levels are a frequent consultation
- Ferritin is increased as an acute phase reactant
  - Infection, inflammation or malignancy
  - Other forms of liver disease
    - Alcoholic liver disease, NAFLD
- Non-HFE iron overload syndromes
  - Ferroportin disease
  - Aceruloplasminemia (very rare)

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## Hemochromatosis: What to do if diagnosis in doubt?

- MRI for hepatic iron assessment
  - Or liver biopsy w/ iron quantification (not simply iron stain)
  - MR elastography may be falsely elevated due to iron deposition
  - Note that MRI will show iron uptake after parenteral iron administration (secondary iron overload syndromes)
- Reasonable to provide therapeutic trial of phlebotomy (cheap, low risk)
  - If patient gets anemic with < 5 phlebotomies; wrong diagnosis

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## Hemochromatosis: ESLD & HCC

- **Advanced fibrosis predicted by older age and ferritin > 1000 ng/mL***
- Look for contributing factors for cirrhosis; concurrent alcohol misuse or viral hepatitis
- HCC uncommon in patients without cirrhosis
  - 30% with HH cirrhosis develop HCC
  - 200X increased risk
  - Risk persists despite iron depletion
- Patients with HFE and cirrhosis should be followed by hepatology

Palmer WC, et al. *J Gen Intern Med* 2018;33(12):2230-6

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## Hemochromatosis: Treatment

- Phlebotomy is the mainstay of therapy
  - Only needed if ferritin elevated
  - Iron chelators inefficient/ineffective for HH
    - Iron chelators needed for secondary iron overload syndromes when patients unlikely to tolerate phlebotomy due to anema
- Two phases: **Depletion** followed by **Maintenance**
  - 500 ml/week (or qow if elderly, small, or CV dz)
  - Check Hgb prior to each phlebotomy
  - Check serum ferritin (±TS) when:
    - Phlebotomy held 3 weeks due to ↓ Hgb, or
    - After 6 months of phlebotomy

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## Hemochromatosis: Treatment (2)

- Maintenance approximately every 3 months (follow ferritin every 6-12 months)
  - Goal: ferritin 50-100 ug/L ± TS% < 50%
- Advise patients to review supplements
  - No iron containing supplements (multivitamin)
  - No high dose vitamin C
- Limited benefit of “low iron” diet

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## Hemochromatosis: Screening

- Population based screening not recommended
- If patient is homozygote, test siblings and adult children
  - Can follow children with iron-studies every several years
    - I do not test minors
  - Due to typical presentation later in adulthood, screening parents typically not needed
- Spousal testing: I do not recommend due to paternity issues
- If non-C282Y hemochromatosis, use iron tests to screen first degree relatives

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## Hereditary Hemochromatosis: Pitfalls

- 10-20% of patients with HH have a negative gene test
  - Non-HFE gene testing available via specialty labs
- Most patients with abnormal iron tests do not have hemochromatosis
  - Especially isolated elevations in ferritin
- Some patients prefer to have disease attributed to a genetic defect they can't control rather than a lifestyle issue

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## Hereditary Hemochromatosis: Non-HFE

| Disorder | Lab Findings | Clinical Features |
|---|---|---|
| TFR2 Hemochromatosis | • Elevated transferrin saturation<br>• Elevated ferritin | • Young presentation (30-40 yrs)<br>• Hepatic, endocrine and CV involvement |
| *HAMP* or *HJV* mutations | • Elevated transferrin saturation<br>• Elevated ferritin | • Severe iron overload phenotype<br>• Very young presentation (15-20 yrs)<br>• Cardiomyopathy |
| Ferroportin Disease | • Low/normal transferrin saturation<br>• Elevated ferritin | • Broad age range<br>• Splenic iron deposition<br>• Liver biopsy shows iron in Kupfer cells |

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## Take Home Points

- Exclude secondary iron overload
- Isolated elevated ferritin often due to inflammatory state
  - Common in NAFLD
- Initial diagnostic test is elevated FASTING transferrin saturation
- Variable penetrance
  - Iron overload rare in non C282Y/C282Y
- Liver biopsy not necessary to confirm diagnosis in most cases

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## Suggested Reading

Diagnosis and Management of Genetic Iron Overload Disorders

- Palmer WC, et al. *J Gen Intern Med* 2018;33(12):2230-6

Haemochromatosis: a clinical update for the practicing physician

- Radford-Smith DE, et al. *Int Med J* 2018;48:509-16

AASLD Guideline: Hereditary Hemochromatosis

- https://www.aasld.org/sites/default/files/2019-06/Hemochromatosis2011.pdf

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