Welcome to the Fall 2024 Carolina Underwriters Forum

Carolina Underwriters Forum

CUF

Agenda

Thursday – October 17, 2024

- **4:30pm Reception**
- **5:30pm Welcome and Updates**
- **5:40pm Speaker Intro and Presentation**

  Dr. Preeti Dalawari

  VP, Medical Director at RGA

  "Iron Overload Disorders"
- **6:40pm Comfort Break and Dinner Buffet**

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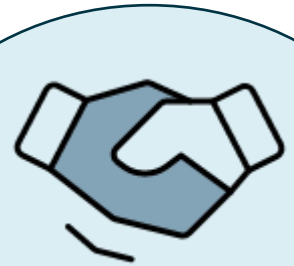

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- UAT/Underwriters Association of Toronto - Sept 11, 2024 - Toronto, Canada
- MUC/Midwest Underwriting Conference – Sept 12-14, 2024 – Cincinnati, OH
- IRUA/Impaired Risk Underwriters Association - Sept 15-17, 2024 - Naples, FL
- TCAHOU/Twin Cities AHOU – Sept 19, 2024 – St. Louis Park, MN
- AHOUCA/Alabama Home Office Underwriting & Claims Association - Sept 19, 2024 - Birmingham, AL
- AAIM/American Academy of Insurance Medicine – Sept 28 - Oct 1, 2024– Montreal, QC, Canada
- LIDMA/Life Insurance Direct Market Association – Sept 29 - Oct 2, 2024 – Phoenix, Arizona
- TWUC/Texas-Wide Underwriting Conference – Oct 2-4, 2024 – Waco, Tx
- Life Affiliates Meeting - Oct 13-Oct 16, 2024 - Chicago, IL
- NEHOUA/Northeast Home Office Underwriters Association – Oct 17-18, 2024 – Portsmouth, NH
- LTCIF/Long Term Care International Forum - Oct 9-11, 2024 - Salt Lake City, UT
- CUA/Chicago Underwriters Association – Oct 10, 2024 – South Barrington, IL
- KC Risk Selectors – Oct 13, 2024 – Lenexa, KS
- ITC/Insurtech Connect - Oct 15-17, 2024, Las Vegas, NV
- CUF/Carolina Underwriters Forum – Oct 17, 2024– Charlotte, NC
- TCAHOU/Twin Cities AHOU – November 7, 2024 – Minneapolis, MN


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Iron Overload Disorders

Hereditary Hemochromatosis

Preeti Dalawari, MD MSPH DBIM FALU
VP and Medical Director
U.S. Individual Life, RGA

October 17, 2024

Overview

01 Iron, Ferritin, and Homeostasis

02 Genetics

03 Work Up and Diagnosis

Case Study

- 42-year-old male
- $1M face amount
- Hereditary hemochromatosis (HH) dx in 2014
- Father had phlebotomies
- 9/22 ferritin 229 but elevated AST
- 9/22 MRI liver with severe parenchymal iron overload and phlebotomies started
- 1/23 MRI liver: minimal iron overload (38)
- 3/24 ferritin 82

Iron

Basics

- Essential trace element for nearly every living organism
- Accepts or donates electrons, making free iron highly toxic

Functions

- Carry or store oxygen
- Catalyze metabolic reactions
- Transport or store the iron itself

Iron

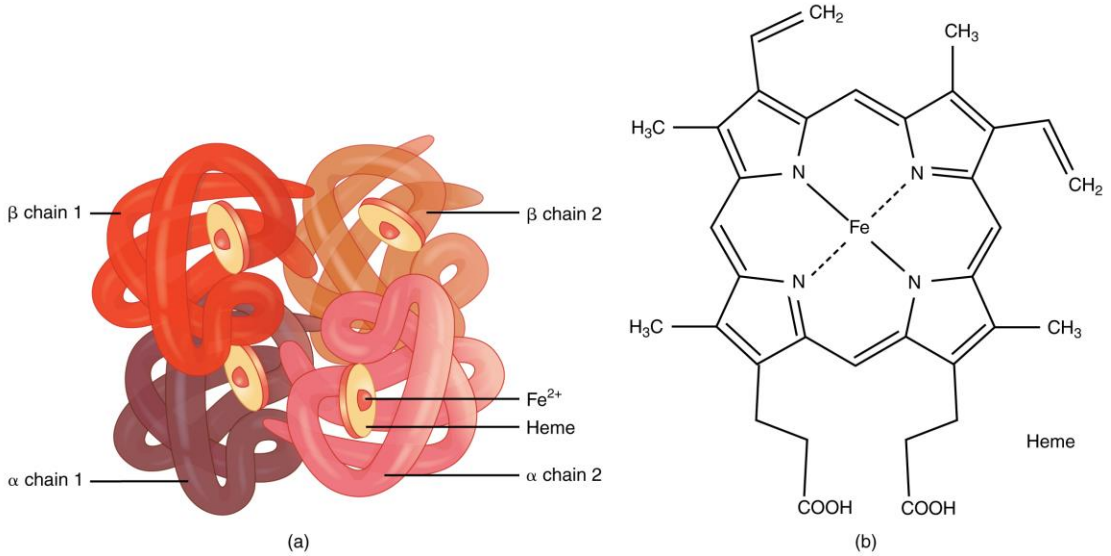
Where is it in the body?

Found in Different Forms

- Normal iron content of body: 3 to 4 grams

- Majority exists as:
  - Hemoglobin in red cells: 2.5 grams (75%)

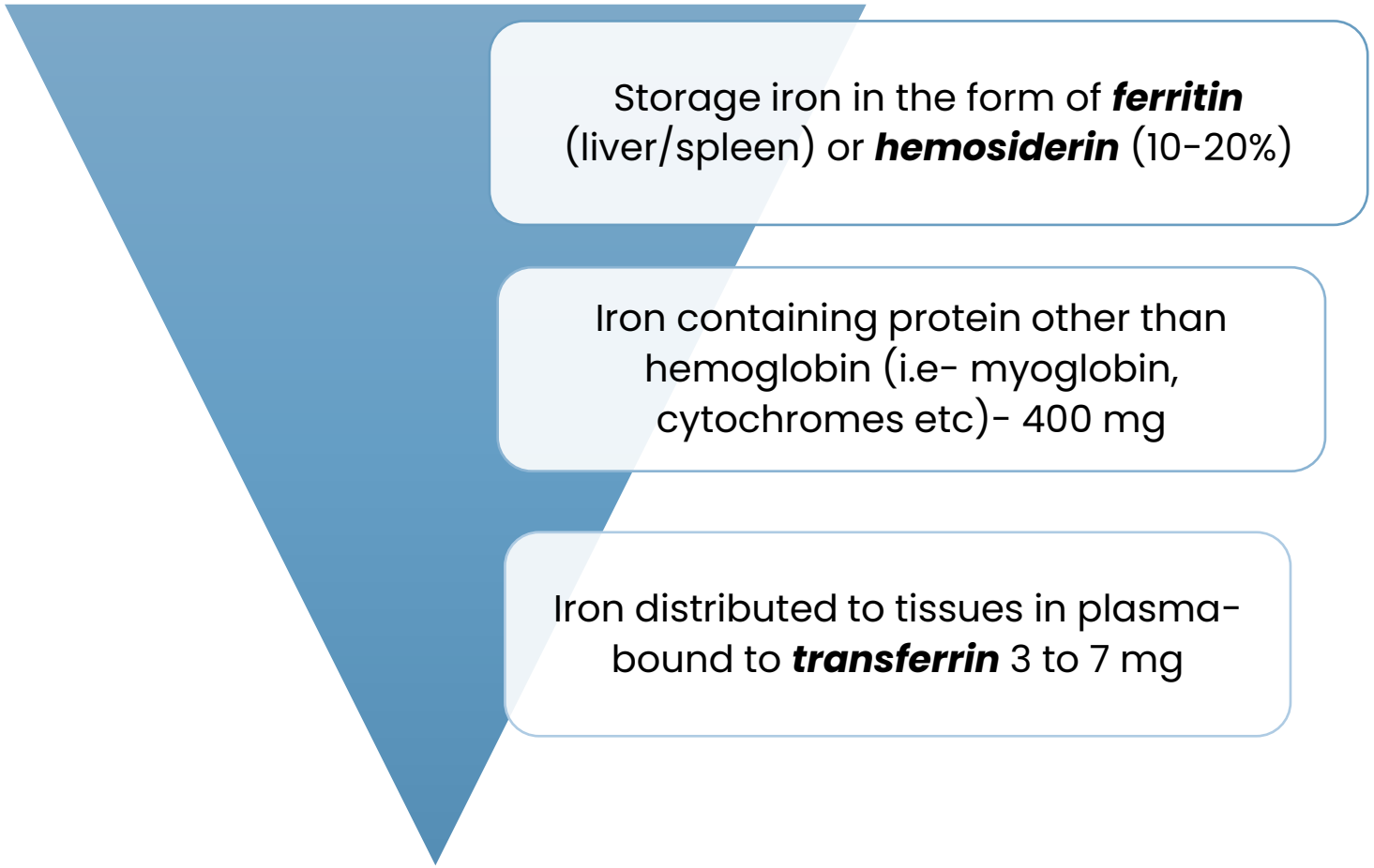
Hemoglobin Structure



http://haemophatic.blogspot.com/2017/03/haemoglobin-synthesis-and-its-catabolism.html

Iron

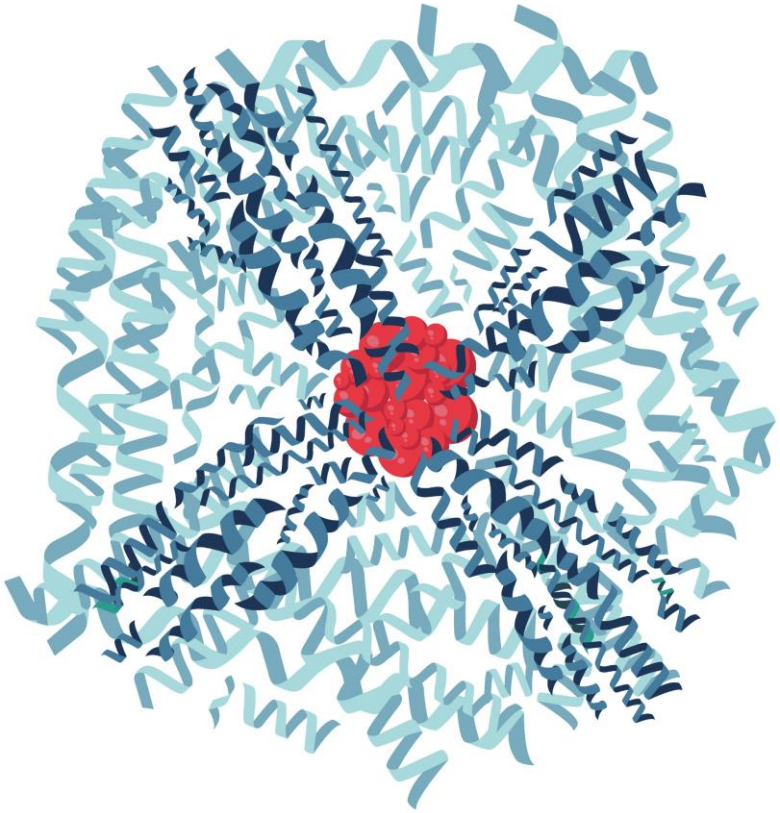
Where else is it in the body?



Ferritin

Iron binding protein

- Both Intracellular and extracellular
- Extracellularly it is known as serum ferritin
- Primary role
  - Iron sequestration in the ferritin mineral core



Knovitch et al. Ferritin for the Clinician. 2009
Adobe stock image

Ferritin

Functions

Chief iron storage protein

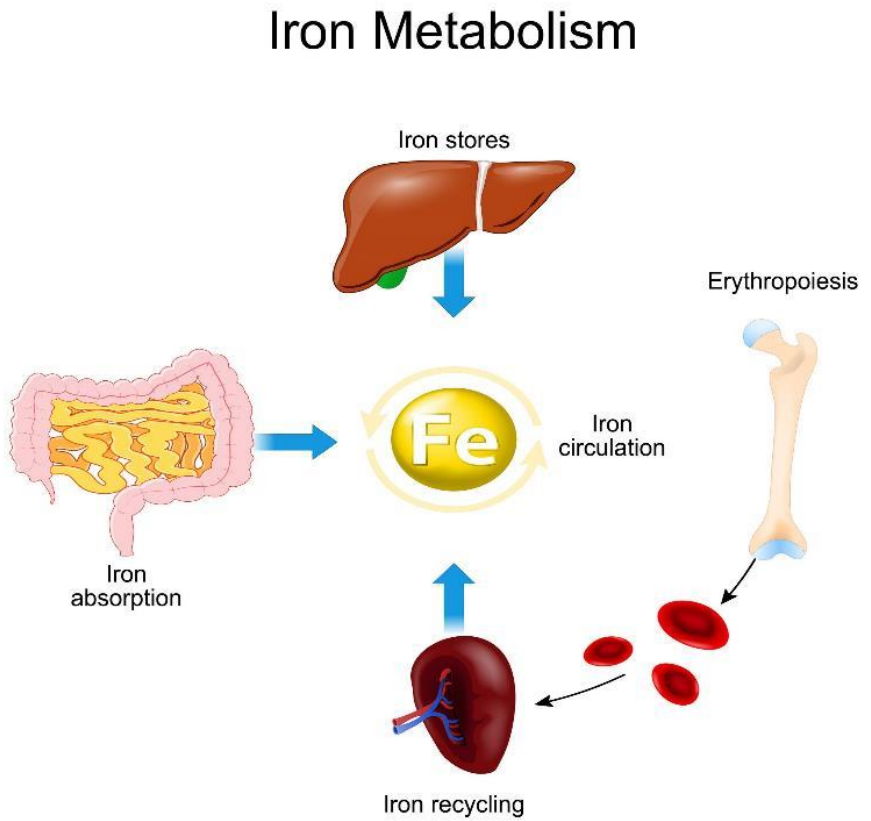
Correlated with total body stores

Used to help diagnose low or high iron states

Acute phase reactant

Iron Homeostasis

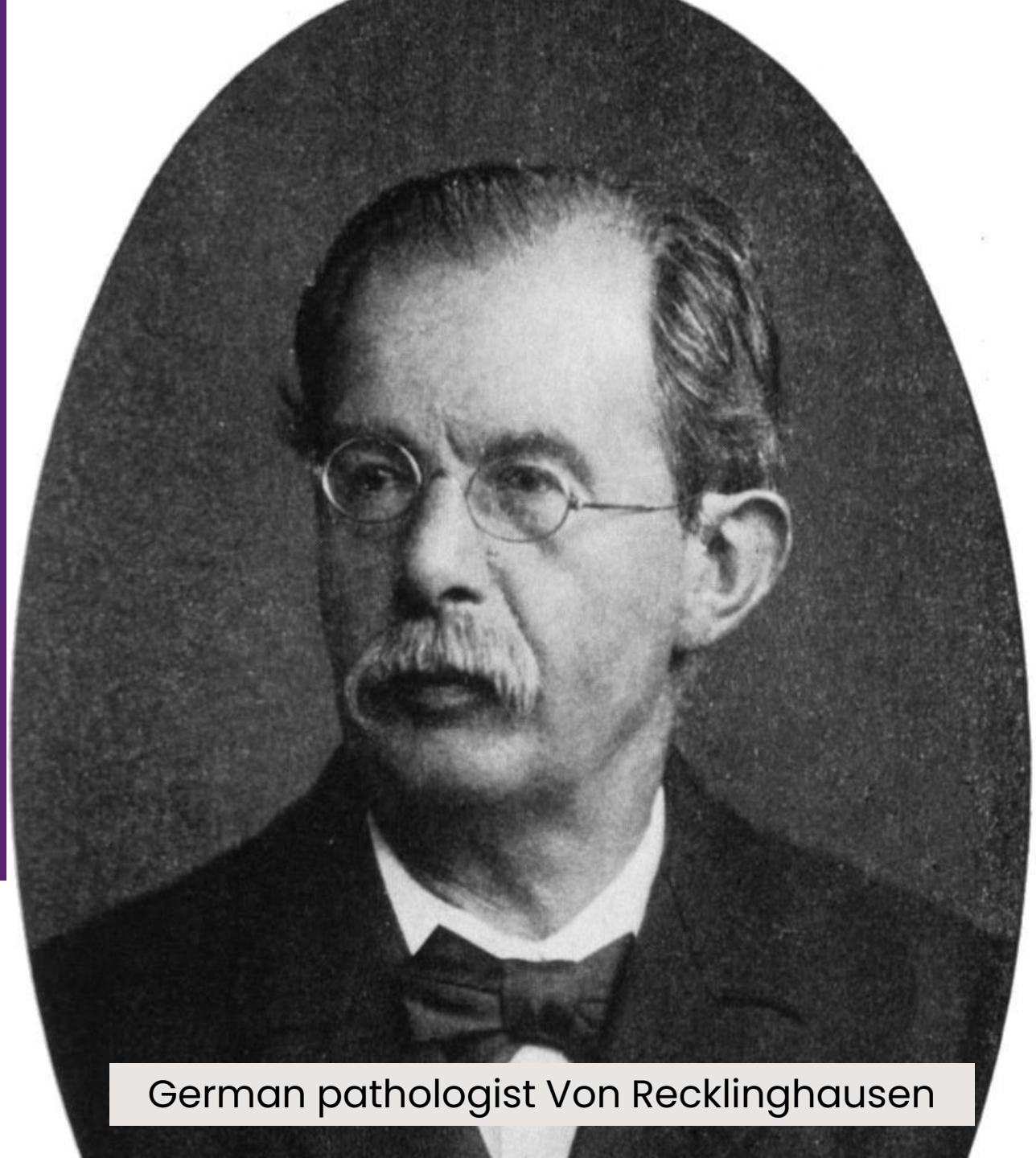
- Iron is integral to the body, but can be highly toxic
  - Majority integrated in globin proteins to help transport oxygen
- Absorbed: Second portion of duodenum in the form of heme and non-heme iron
  - Regulated at this intestinal level
  - No physiologic avenue to *excrete* excess iron



Hepcidin - amino acid peptide produced mainly in the liver

Key regulator of iron stores by inhibiting iron absorption

Hereditary Hemochromatosis



German pathologist Von Recklinghausen

https://upload.wikimedia.org/wikipedia/commons/9/97/Friedrich_Daniel_von_Recklinghausen.jpg

Prevalence

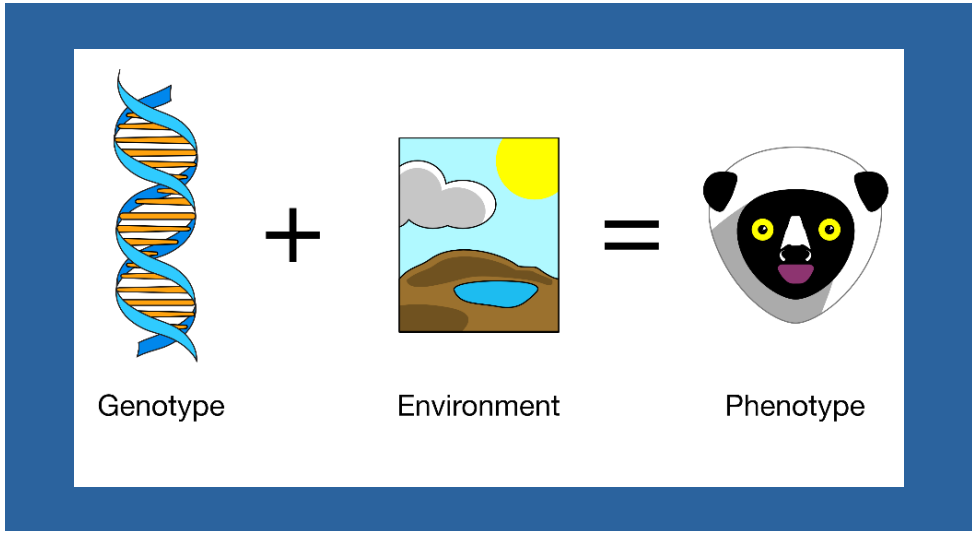
Hereditary hemochromatosis

Considerations

- One of the most common genetic disorders in the U.S. (type 1) and the world
  - (1 in 300 non-Hispanic whites in the U.S. and 1 in 500 people of NW European ancestry)
- Autosomal recessive *with low penetrance*
- **Not all people with HFE mutations develop iron overload and clinical HH**
- Other genetic, environmental factors, medical conditions, dietary intake, blood loss have a role in iron overload

Considerations

- Genotype
- Phenotype--→ clinical penetrance
- Lab data--→biochemical expression



Genetics

HFE gene: High Fe gene

HFE gene function

- Produces a HFE protein located on surface of cells, primarily liver and intestinal cells
- HFE protein regulates production of *hepcidin*

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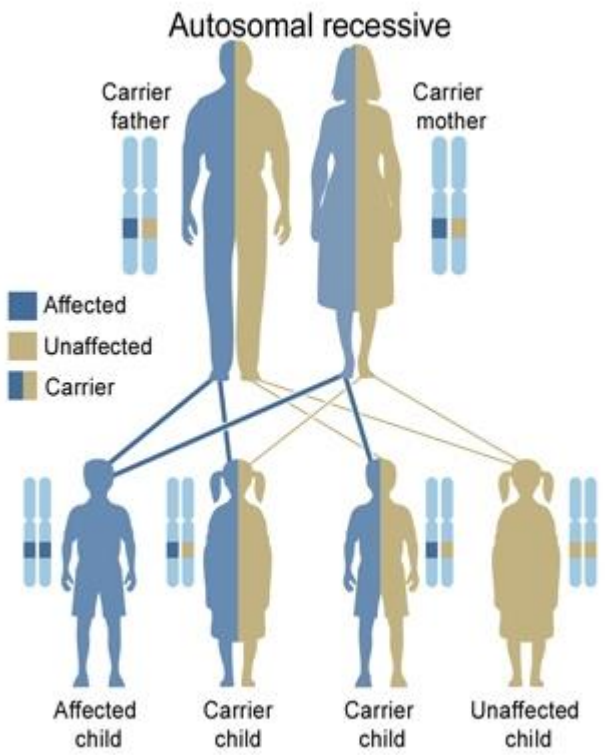
Mutations cause low hepcidin levels, and thus result in increased iron intestinal absorption

Quick Genetic Review

Genotype

- Genetic characteristics
- Homozygotes:
  - C282Y/C282Y
  - H63D/H63D
  - S65C/S65C
- Compound Heterozygotes:
  - C282Y/H63D
  - C282Y/S65C

Autosomal Recessive



Phenotype

- Physical characteristics
  - Iron overload vs. non-iron overload state
  - Complications/iron depositions

(clinical penetrance)

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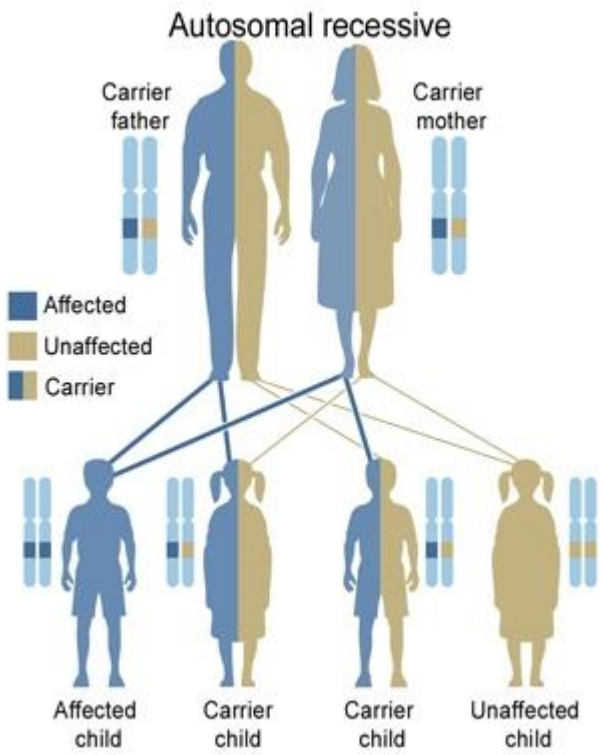

Phenotype

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  - Iron overload vs. non-iron overload state
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(clinical penetrance)

Carriers typically do not manifest iron overload!

HFE Genetic Mutation

Subtypes: 95% of inherited cases

Classification	Genes Involved	Inheritance	Protein Involved
Type 1A	Homozygous: C282Y/C282Y	AR	Hepcidin
Type 1B	Compound Heterozygous: 1. C282Y/H63D	AR	Hepcidin
Type 1C	Mutation S65C	AR	

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80-90%

Non-HFE Genetic Mutations

5% of inherited case

Classification	Genes Involved	Inheritance
Type 2A juvenile	HJV	AR
Type 2B juvenile	HAMP	AR
Type 3	Transferrin receptor 2	AR
Type 4A	Ferroportin (FPN1)	AD
Type 4B	Ferroportin (FPN1)	AD

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Phenotype

Symptoms and complications

Clinical Presentation

- Nonspecific symptoms:
  - Fatigue
  - Arthritis
  - Hypogonadism/pituitary
  - Liver most affected organ

Liver

- Variable:
  - Asymptomatic
  - Elevated LFTs
  - RUQ pain
  - Complications of ESLD
  - Some with no clinical Sx, have hepatic iron overload

Phenotype

Liver

Cirrhosis Rate in Patients with HH

Elevated Serum Ferritin >1000	Elevated ALT or AST	Platelet Count <200	Excessive Alcohol Use	Cirrhosis Rate
No	No	No	No	0
Yes	No	No	No	20-45%
Yes	Yes	Yes	No	80%
Yes	Yes	Yes	Yes	>80%

Hepatocellular Carcinoma

- In setting of cirrhosis
- Chief cause of death in 30-45% of those with cirrhosis
- Screening with ultrasound similar to other causes of cirrhosis
- Some recommend to screening q2-3 years in those initially dx with sf >1000

Risk of cirrhosis rises with ferritin >1000
Lifetime risk is 10% in untreated HH in men

Phenotype

Heart and pancreas

Nonischemic Cardiomyopathy

- More common in non HFE genetic mutations
- Not as common in type 1 HH, but second leading cause of mortality
- Poor correlation between serum ferritin and cardiac function
- Restrictive or dilated CM, arrythmia, heart failure, SSS, Atrial fibrillation
- Recent study only 1-3% had CM

Diabetes

- Pathogenesis is multifactorial
- Seen in 13-23% of those with type 1 HH

Diagnosis

Labs

Suspected iron overload

Key players

- Clinical History
- CBC
- LFTs
- Iron studies:
  - Iron
  - **Ferritin**
  - Transferrin (reported as TIBC)
  - **TSAT (transferrin saturation)**

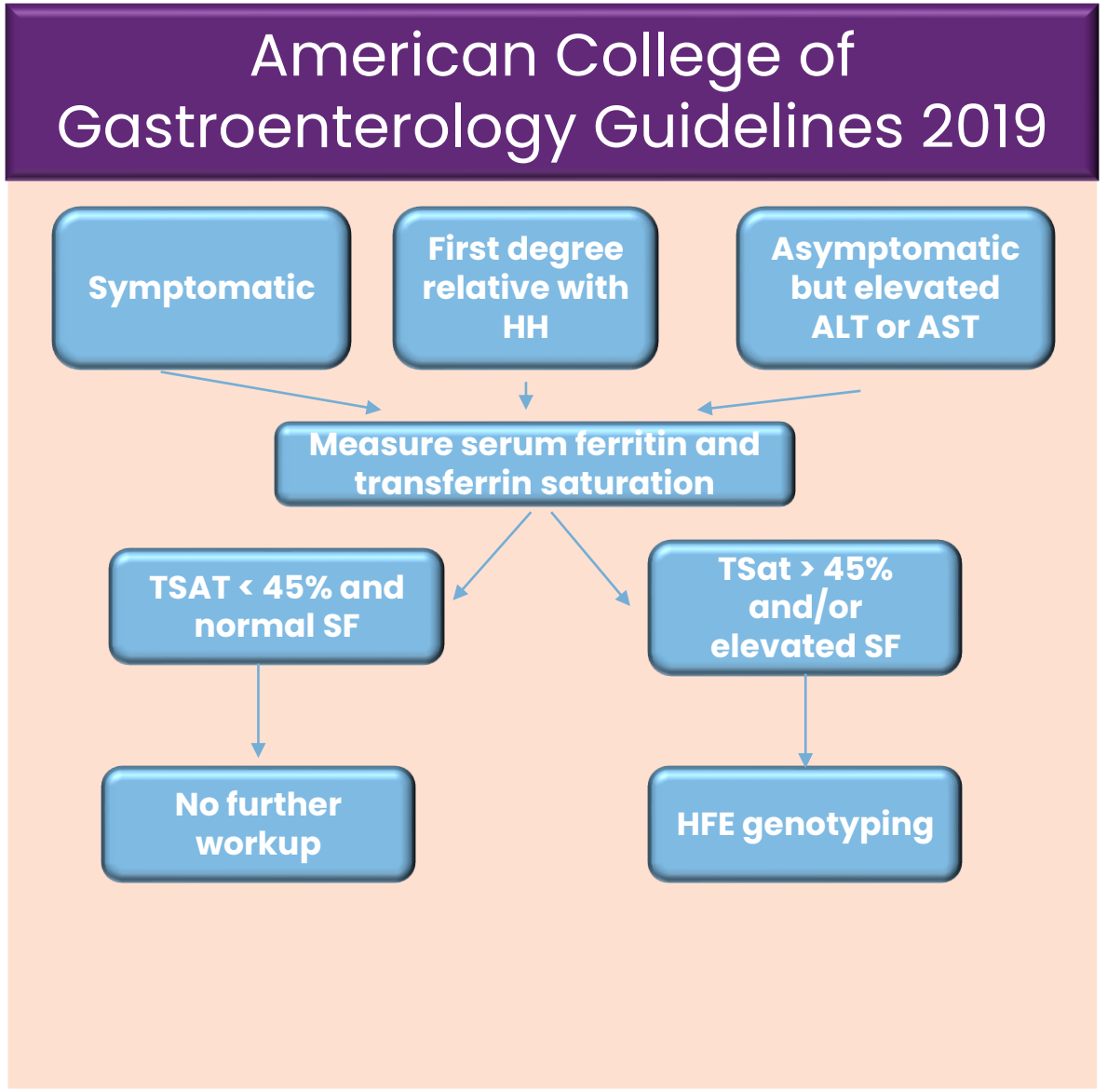
- Transferrin
  - Produced by liver
  - main protein that binds iron and *transports* it throughout the body

- Transferrin saturation
  - % saturation = transferrin saturation = total iron/TIBC
  - How many of the transferrin iron binding sites are occupied by iron
  - **Normal TSAT 25-35%**

Diagnosis

Biochemical expression

- Labs
  - CBC, LFTs, and iron studies (iron, TIBC, TSAT)
    - **Elevated ferritin and TSAT greater than 45-55%**
- Rule out other causes
- Genotype
- MRI
- Other tests
  - Liver biopsy
  - Response to phlebotomy
  - Endomyocardial biopsy



T2 Weighted MRI

Noninvasive measure of hepatic iron content

- Loss of signal intensity in the liver
- Depositions in reticuloendothelial areas help to distinguish different HH types as well as secondary iron overload
- Hepatic Iron abnormal >36 micromole/g

https://upload.wikimedia.org/wikipedia/commons/9/97/Friedrich_Daniel_von_Recklinghausen.jpg

Treatment for C282Y Homozygotes

Phlebotomy

- **Elevated ferritin levels should be treated, regardless of symptoms**
- Each 500mL phlebotomy withdraws 250 mg of iron
- Weekly or every 2 weeks → ferritin to 50-150 ug/L (as long as not anemic)
- Maintenance
  - Hgb should not be <11 g/dL
  - Varies from monthly to annually depending on patient
- May improve liver fibrosis (in 30% of cases); cardiac dysfunction, skin hyperpigmentation, arthropathy, and pancreas variable effected
- Alternative: iron chelation therapy

Mortality Implications

- Survival has improved over time
- Dx with 1996 and 2010 (and treated) calculated SMR: 0.94
- With cirrhosis, all cause mortality: SMR 4.43
- Untreated, with expressed clinical phenotype have higher mortality than general population

Underwriting Considerations

Lucky for us

The genotype matters less than the phenotype.

- Do we have a documented diagnosis of hereditary hemochromatosis?
  - Heme/gi/pcp records stating such
  - Evidence of yearly checks (esp. if SF wnl)
  - Phlebotomy
  - LFTs
  - Symptoms/comorbid conditions (or secondary hemochromatosis workup)

Case Study

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Case Conclusion

- Family history of HH
- Severe iron overload on MRI
- Getting phlebotomies
- Current LFTs ok and ferritin controlled
- Repeat MRI with decrease in deposition of iron

Case Study

- 50 yo M
- FA for 2 million
- Hx: OSA on CPAP, Fatty liver, dx with Covid, not hospitalized
- 2 week visit after Covid, labs checked:
  - **Ferritin 613**
  - Iron 107 (50-180 mcg/dL)
  - TIBC 311 (250-425 mcg/dL)
  - **% saturation 34%** (20-48%)
  - Transferrin 252 (188-341 md/dL)
  - Hgb/hct 15.2/45
- Hep B and C negative
- LFTs normal

PCP assessment: hemochromatosis

Key Takeaways

- ☑ Worry less about the genotype. Focus on the phenotypic and biochemical expression.
- ☑ While compound heterozygotes by itself is not expected to have a severe form for iron overload, comorbid conditions can lead to this phenotype (see above).
- ☑ Suspect HH when ferritin *and* TSAT are elevated – look for both these or hematology/gi records.
- ☑ If ferritin is normal in dx HH, then yearly ferritin levels should be checked.
  Treatment is recommended even if only mildly elevated.

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Questions?

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