Iron!!

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GENERAL HEMATOLOGY
OHSU

DISCLOSURE

Relevant Financial Relationship(s)

Author: UpToDate (Iron def, anemia in pregnancy)

Iron Deficiency

- Common!
  - 14% US Adults
  - 38-80% US Menstruating women
  - 80% 3rd trimester pregnancies
- Treatable!

Other Effects of Fe Deficiency

- Iron is important in a variety of enzyme system
- Muscle second greatest user of iron
- CNS iron also important
- Iron deficiency important above and beyond just anemia

Iron for Fatigue

- Two RCT with oral iron show benefit with ferritin < 50 ng/mL
- Should be considered for fatigue and ferritin < 50 ng/mL

BMJ. 2003 May 24;326(7399):1124
CMAJ 184:1247-1254, 2012

Psych and Cognitive

- 1408 in 18 studies
- RCT iron improved: anxiety, fatigue, well being, cognition and short term memory
- Neurosci Biobehav Rev. 2025

Iron in Kids

- Babies born to mothers iron deficient (ferritin < 30 at 15 weeks) at age two years had lower language and motor skills
- J Nutrition 2025

Iron and Athletes

- Low iron even without anemia affects performance
  - Decrease muscle stores?
- Consider screening female athletes
- Check fatigued athletes
- RCT show improvement in performance treating non-anemic iron deficiency

Other Effects of Low Iron

- Restless legs
  - Ferritins < 100 ng/mL
  - Lack of CNS Iron
- Alopecia
  - Ferritins < 100 ng/mL
- Pulmonary hypertension
- Heart failure
- Acute mountain sickness

Don’t Wait for Anemia!

Anemia is end stage iron deficiency!

Statistical Iron Deficiency

- Laboratory values for ferritin reflect arbitrary criteria and not physiology
- Ranges of "normal" unrealistic for:
  - Women
  - Older patients

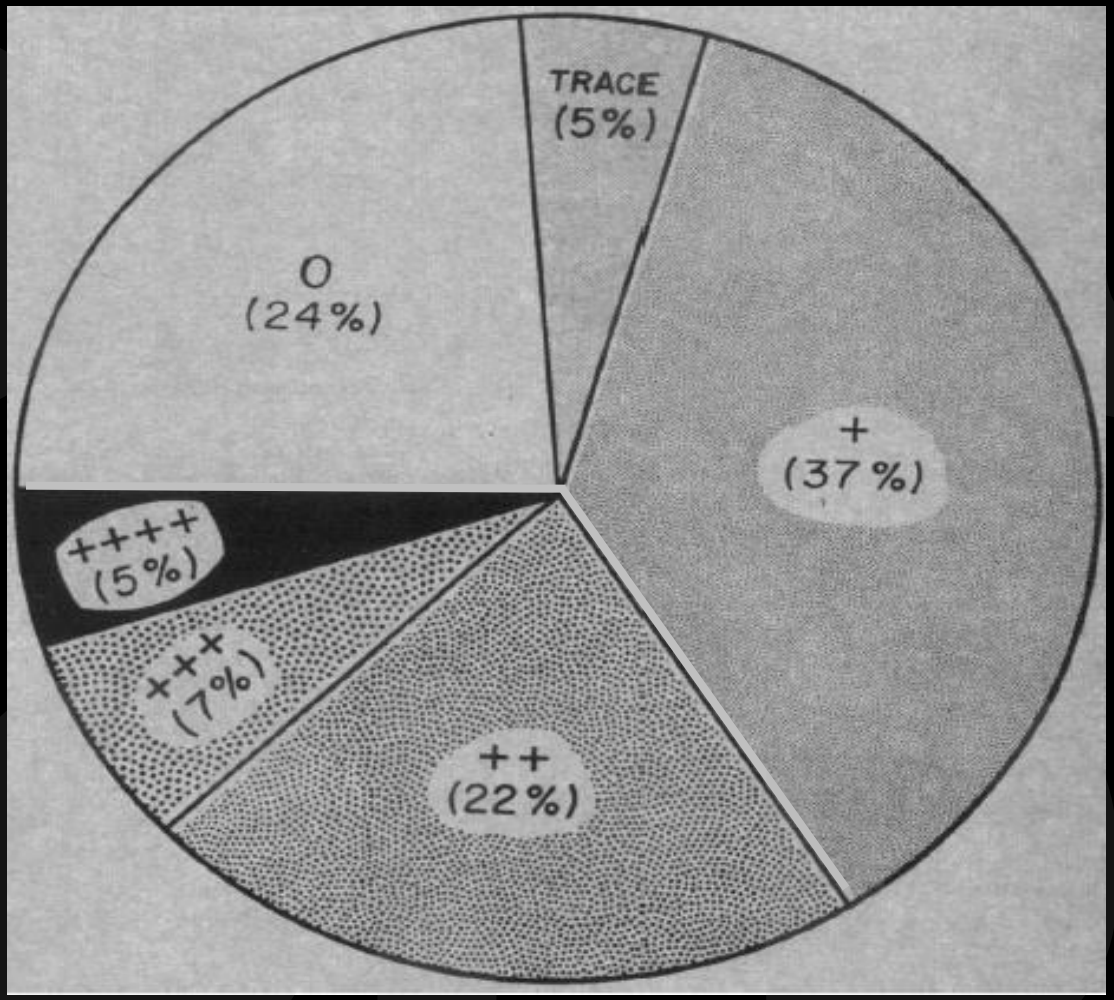
Women and Iron

- No physiologic reason that women should have different ranges of normal for ferritin
  - 85% of 20 year old men have ferritin over 50 ng/mL
  - 25% of 20 year old women do
- Often overlooked cause of fatigue
  - Benefit of raising ferritin > 50 ng/mL

Iron Requirements

- Men:
  - ~ 1mg/day loss
  - RDA: 8mg iron
  - Daily intake: 16-18 mg/day
- Women:
  - ~2.4-3.4 mg/day loss
  - RDA: 18 mg iron
  - Daily intake: 12.6-13.5 mg/day

Most Women have Low Iron Stores

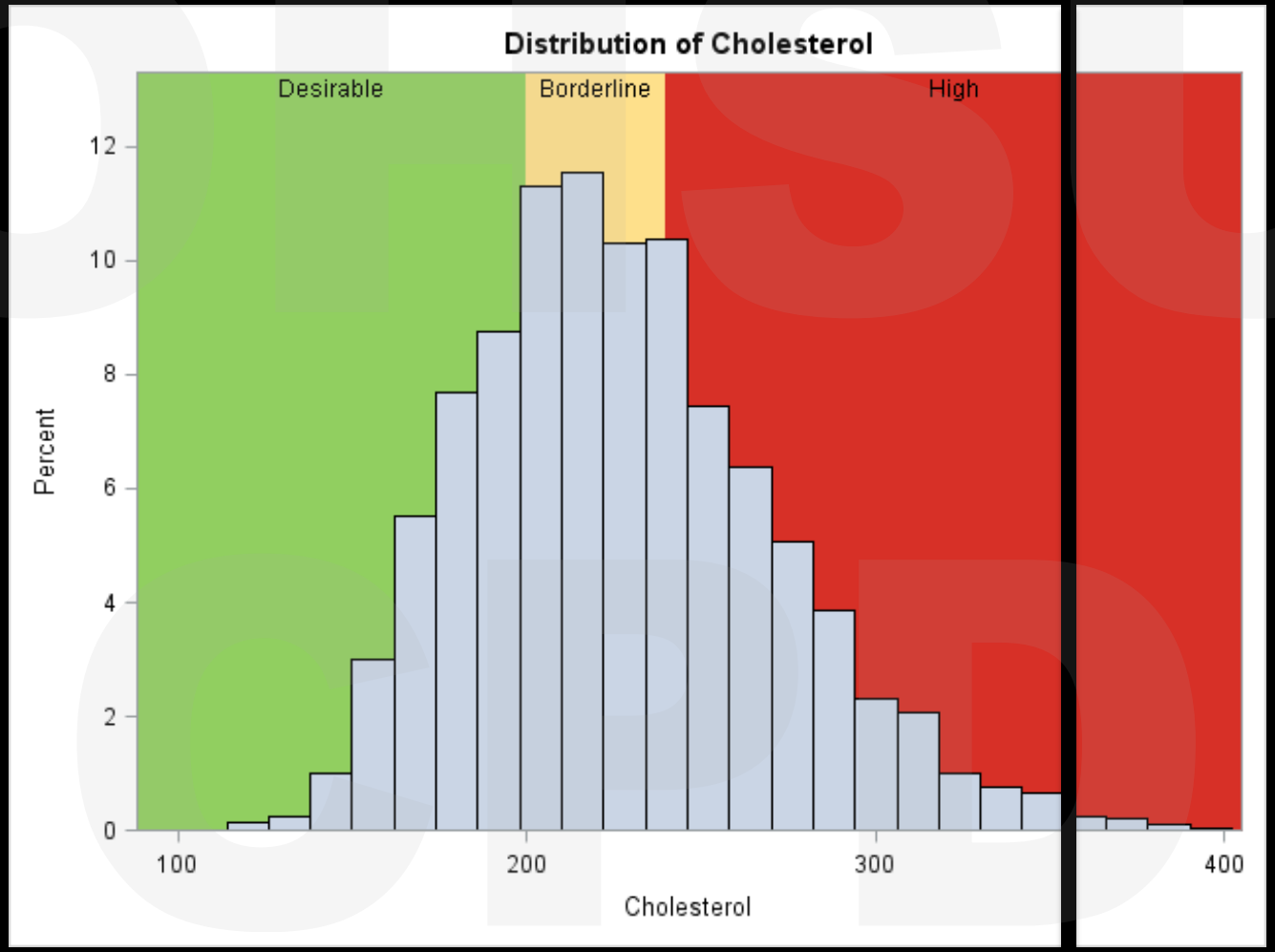


JAMA, Mar 1967; 199: 897 - 900

Most Women have Low Iron Stores

- Puolakka: 50% absent iron stores, 15% scant stores
- Hallberg: 34% absent iron stores
- Rybo: 31.5% absent iron stores, 14.3% scant

Acta Obstet Gynecol Scand Suppl. 1980;95:35-41
Br J Haematol. 1993;85(4):787-798
Scand J Haematol Suppl. 1985;43:5-39



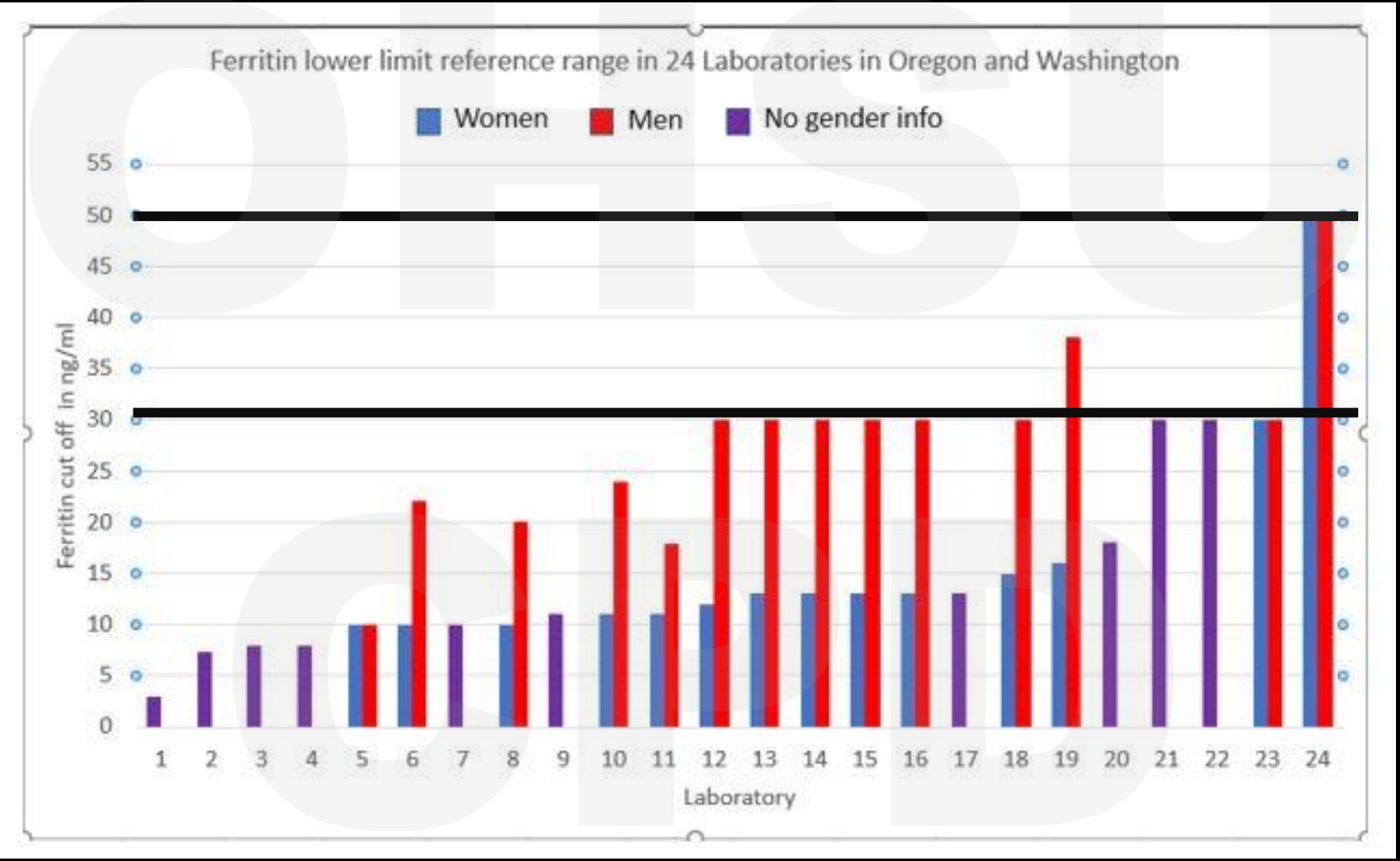
https://blogs.sas.com/content/iml/2015/12/09/categories-histogram-block-plot.html

Ferritin Lower Limit

- Two RCT show treatment < 50 ng/dl improves outcomes
- GI iron absorption only returns to normal at ferritins of 50-60 ng/dl
- 50 ng/dl natural cut-off?
- 30 ng/dl – best sensitive/specificity

ASH Guidelines

- 20 ng/ml – 9 months to 4 year
- 30 ng/ml – general population
- 50 ng/ml – if symptoms



Dr Merav Sendowski, Alaska Rosenfeld

Iron Deficiency – Common!

- Prevalence of iron deficiency
- 15 µg/L: 17% (15.4%-19.2%)
- 30 µg/L: 38.6% (35.8%-40.9%)
- 50 µg/L: 77.5% (75.7%-79.3%)

- JAMA. 2023;329(24):2191-2193.

Especially in Pregnancy/

Ferritin	15	20	33
< 15 ug/L	4.5%	13.7%	51.2%
< 30 ug/L	20.7%	43.7%	83.8%

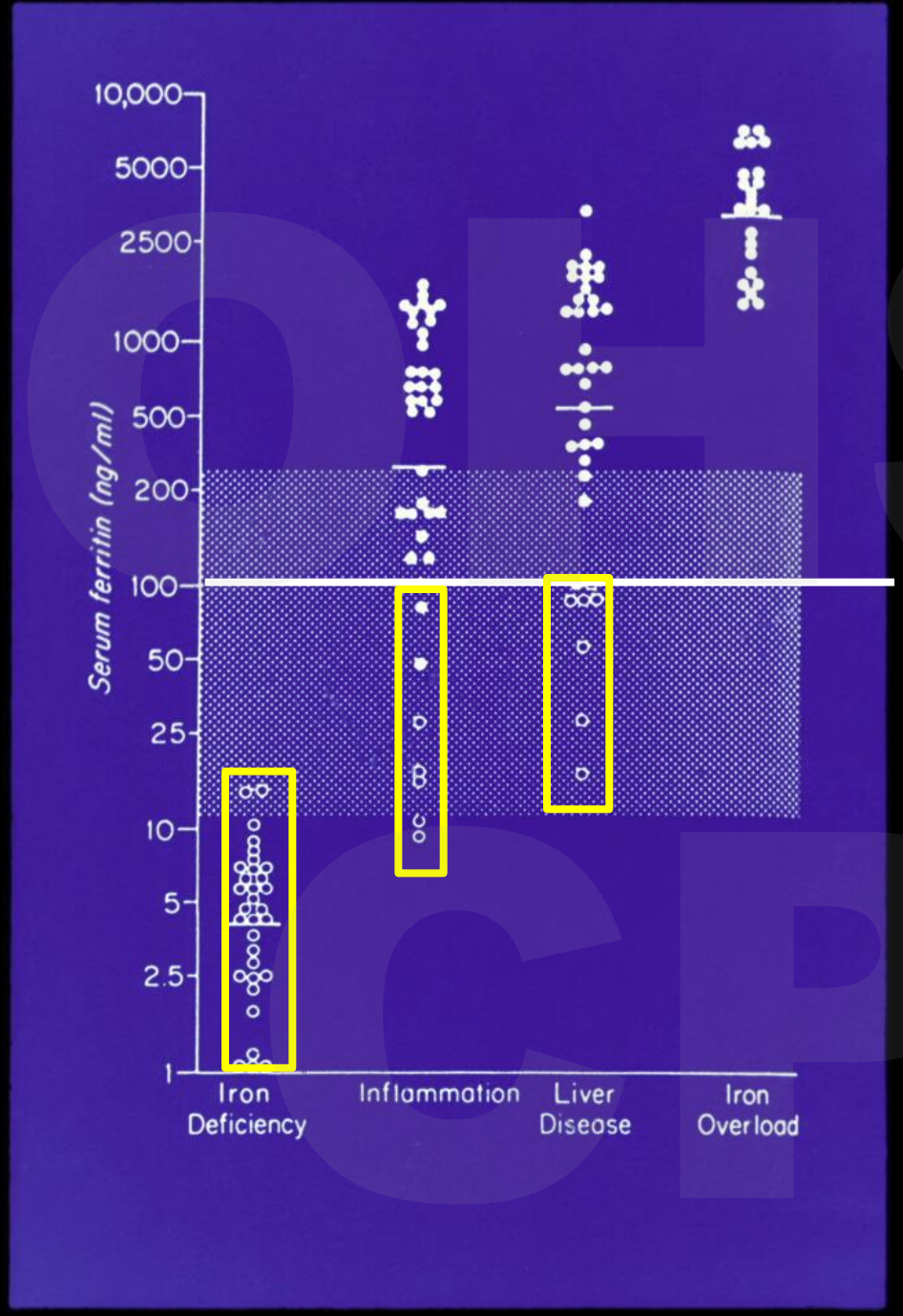
Note: ASH specifically recommends *against* using ferritin of 15 ug/l as a cutoff

Am J Clin Nut 120:1259, 2024

Testing for Iron Deficinecy

Serum Ferritin

- Serum ferritin proportional to iron stores
- Needs iron to be produced
  - –Acute phase reactant only in presence of iron
- Most accurate non-invasive test of iron stores!



N Engl J Med. 1974 May 30;290(22):1213-6.

Iron Deficiency

- Serum ferritin is BEST non-invasive test of iron status
  - > 100 ng/mL rules out iron deficiency
  - Lower limit changes with age and condition
    - Patient over 65 with ferritin < 50 ng/mL all iron deficient

Ferritin: Bottom Line

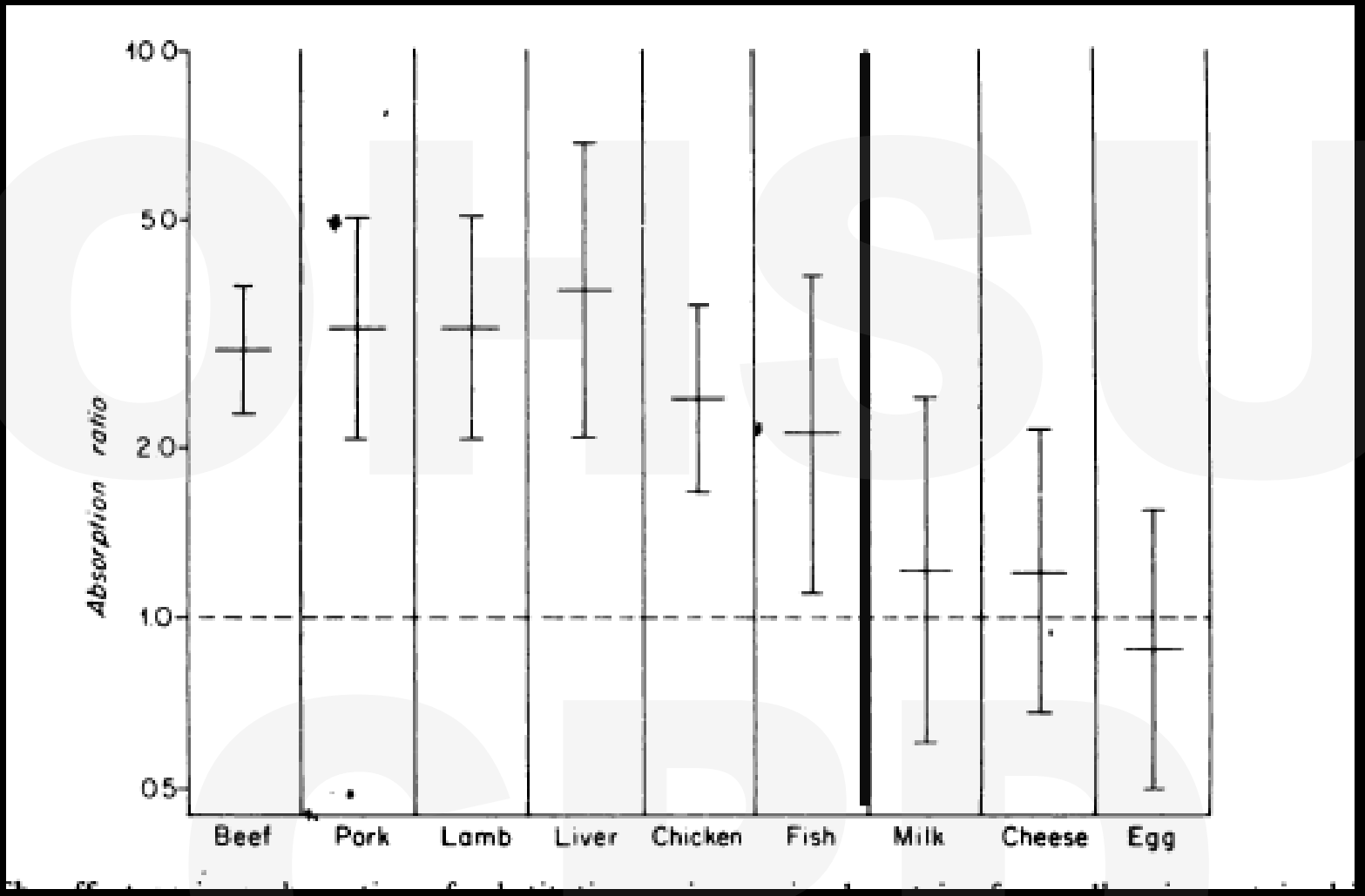
- Ignore lab reference ranges!
  - < 15 ng/ml 100% specific
    - But very very insensitive
  - < 30 ng/ml – many guidelines
  - < 50 ng/ml cut-off physiologic
  - > 100 ng/ml rules-out

IF YOU WANT YOUR CHILDREN
TO BE
HEALTHY & STRONG

GIVE THEM
IRON BITTERS

Dietary Iron

- Heme iron 10x better absorbed than non-heme iron
- Meat protein improves iron absorption



Am J Clin Nutr **August**
1976 vol. 29 no. 8
859-867

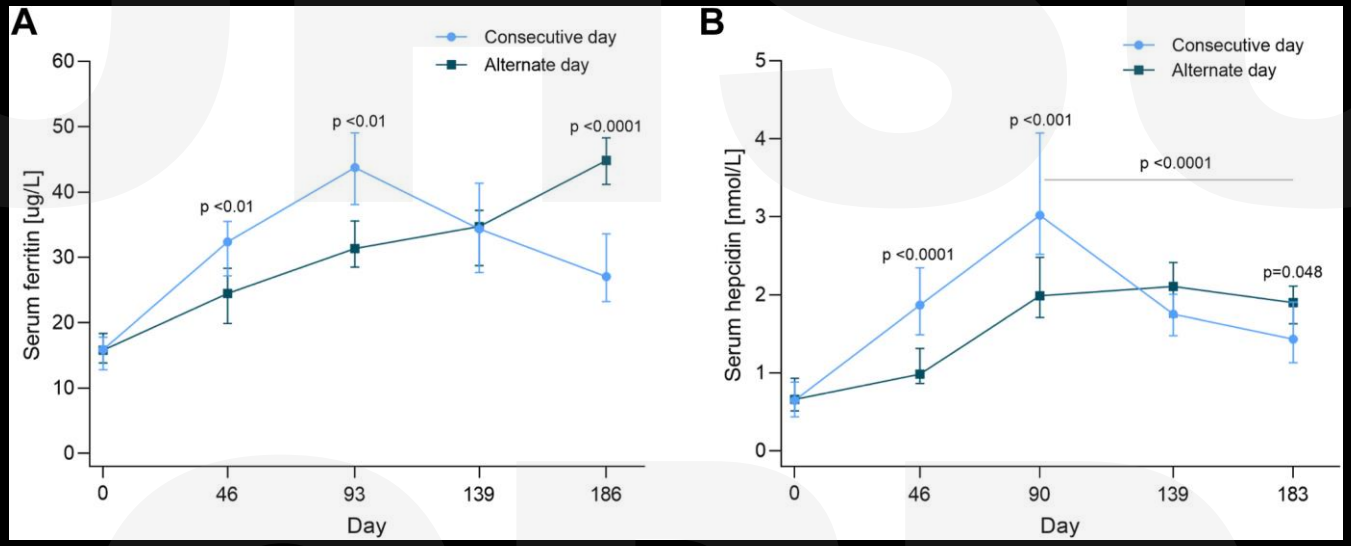
Dietary Iron

- Calcium, fiber can block iron absorption
  - Overcome by vitamin C
- Tea decreases 75-80%
- Coffee decreases 60% (5 oz!)

Oral Iron Pills

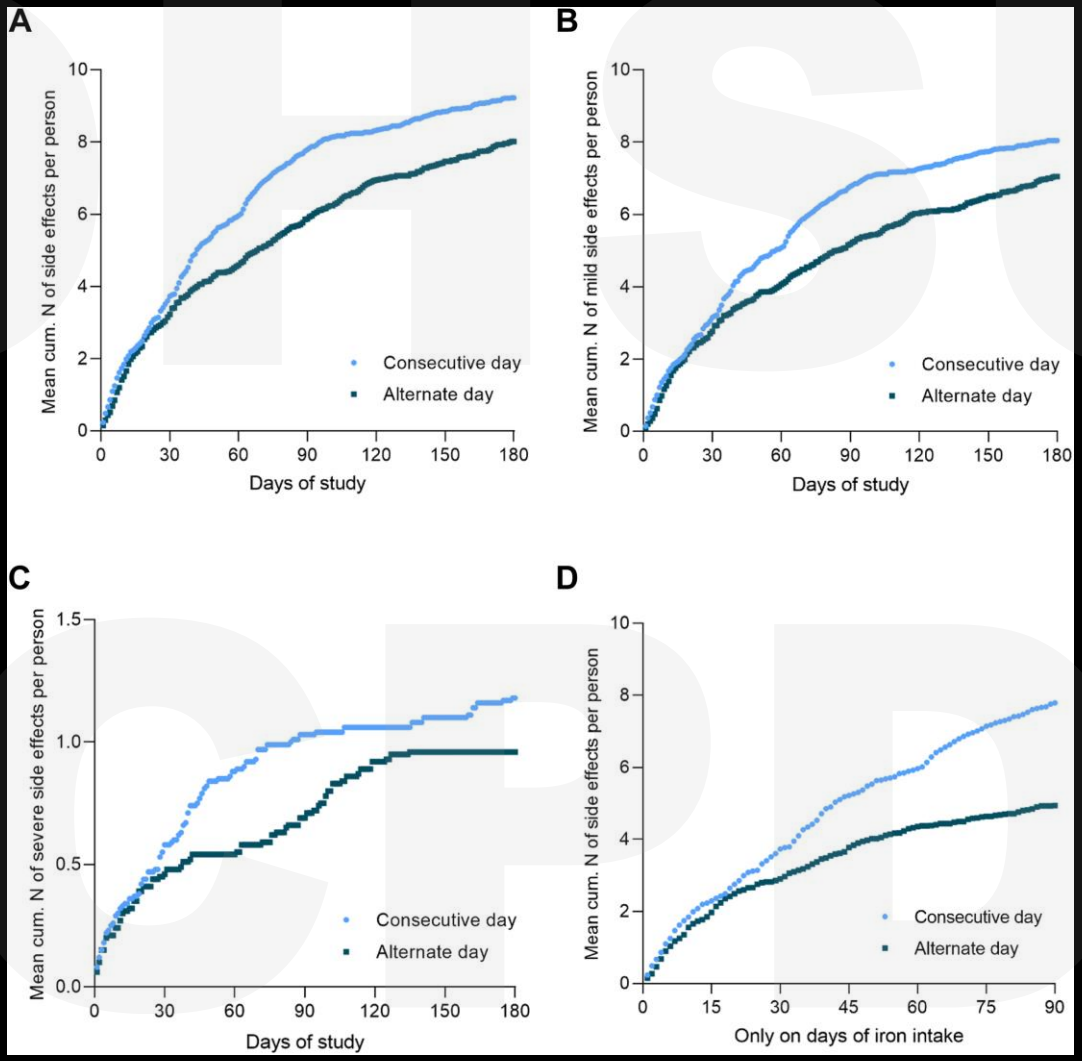
- Gut can only absorb a limited amount of iron
- Maxed out at ~ 10mg

Every day vs Every Other Day



eClinicalMedicine 2023 65DOI: (10.1016/j.eclinm.2023.102286)

Every day vs Every Other Day



eClinicalMedicine 2023 65DOI: (10.1016/j.eclinm.2023.102286)

Alternate Day Iron

- Summary of studies
- Every day faster improvement
- Every other day better tolerated

What I Do

- Cheapest iron pill
  - Ferrous sulfate
- Once a day with meals
  - Vitamin C 500
  - No tea or coffee for one hour after
- If intolerant can try lower dose

Etiology of Iron Deficiency

- All iron deficiency has a cause!
- Blood loss must always be assumed!

Contributors to Iron Deficiency

- GI
  - NSAIA 10-15%
  - Colon Ca 5-10%
  - Gastric Ca 5%
  - Ulcers 5%
  - Angiodysplasia 5%
  - Esophagitis 2-4%
  - Esophageal Ca 1-2%
- Non-GI
  - Menstruation 20-30%
  - Celiac disease 4-6%
  - Bariatric surgery 1%

HMB

- European survey
  - 27.2% with 2 or more HMB symptoms
  - 46% never consulted physician
- Runners
  - 22% HMB
    - 48% with severe iron deficiency
- Athletes
  - 43.5% HMB
    - 51% with iron deficiency

Int J Ob GYN 128:196, 2015, Anaeth 76(s4)56, 2021, Medicine 100:1, 2021

Iron Deficiency: GI Evaluation

- Most patients with identifiable source of GI blood loss
- Very high number with tumors
- Who to evaluate?
  - 2021 AGA guidelines “any iron deficiency anemia”

GI Evaluation

- Moving target
- Any Man
- Women
  - > 40
  - + symptoms
  - + family history colon cancer
  - Recurrent iron deficiency

Parental Iron Therapy

- When to use
  - Refractory to oral iron
  - Unable to take oral iron
  - Cannot keep up with blood loss
    - Bariatric surgery
    - Inflammatory bowel disease
    - Chronic GI bleeding

OHSU Data (Any Reaction %)

- Minor infusion reactions common (~1-2%) but true anaphylaxis very rare
  - LMW Iron Dextran 3.8
  - Ferric Carboxymaltose 1.4
  - Iron Sucrose 4.3
  - Ferumoxytol 1.8
- Severe reactions: 1:15,000 infusions
- ~ 35,000 doses
- JAMA Open 2022

Dosing IV Iron

- Replacement formulas inaccurate
- Give ~1000mg
  - Recheck in 4 weeks
  - If severe anemia recheck in two weeks

IV Iron Dosing

Formulation	Recommended Dose
LMW Iron dextran	1000mg over 1 hr
Ferumoxytol	510 x 2 or 1020 over 15 min
Ferric carboxymaltose	1000mg over 15 min or 750 mg x 2
Iron isomaltoside	1-2000 mg over 15 min

Remember!

- Iron is good!
- Ferritins > 50 ng/mL are good
- Oral iron
  - One pill/day
  - With vitamin C
  - With meat if feasible
- Don’t be afraid of IV iron

High Iron Labs: What to Do

- High iron saturations
- High ferritins

High Iron Saturation

- Can be influenced by oral iron
- Need to repeat fasting for 5-9 hours

High Iron Saturations

- Hemolysis
  - Release of heme iron
- Iron overload
  - Genetic
  - Acquired
- Don’t get too worked up if ferritin is normal

Ferritin

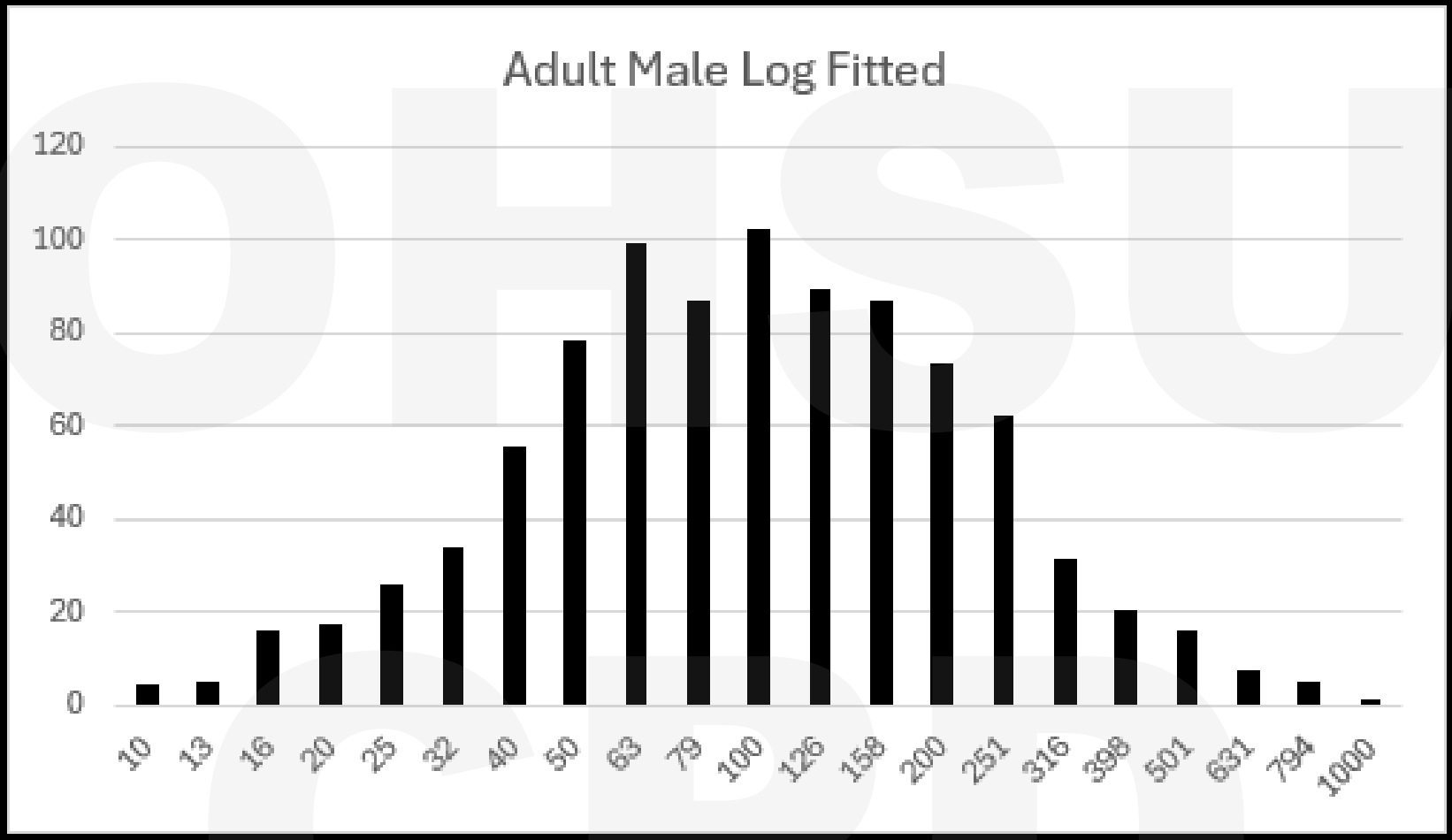
- Elevated levels
  - Inflammation
  - Liver disease
    - Fatty liver
  - Iron overload

Inflammation

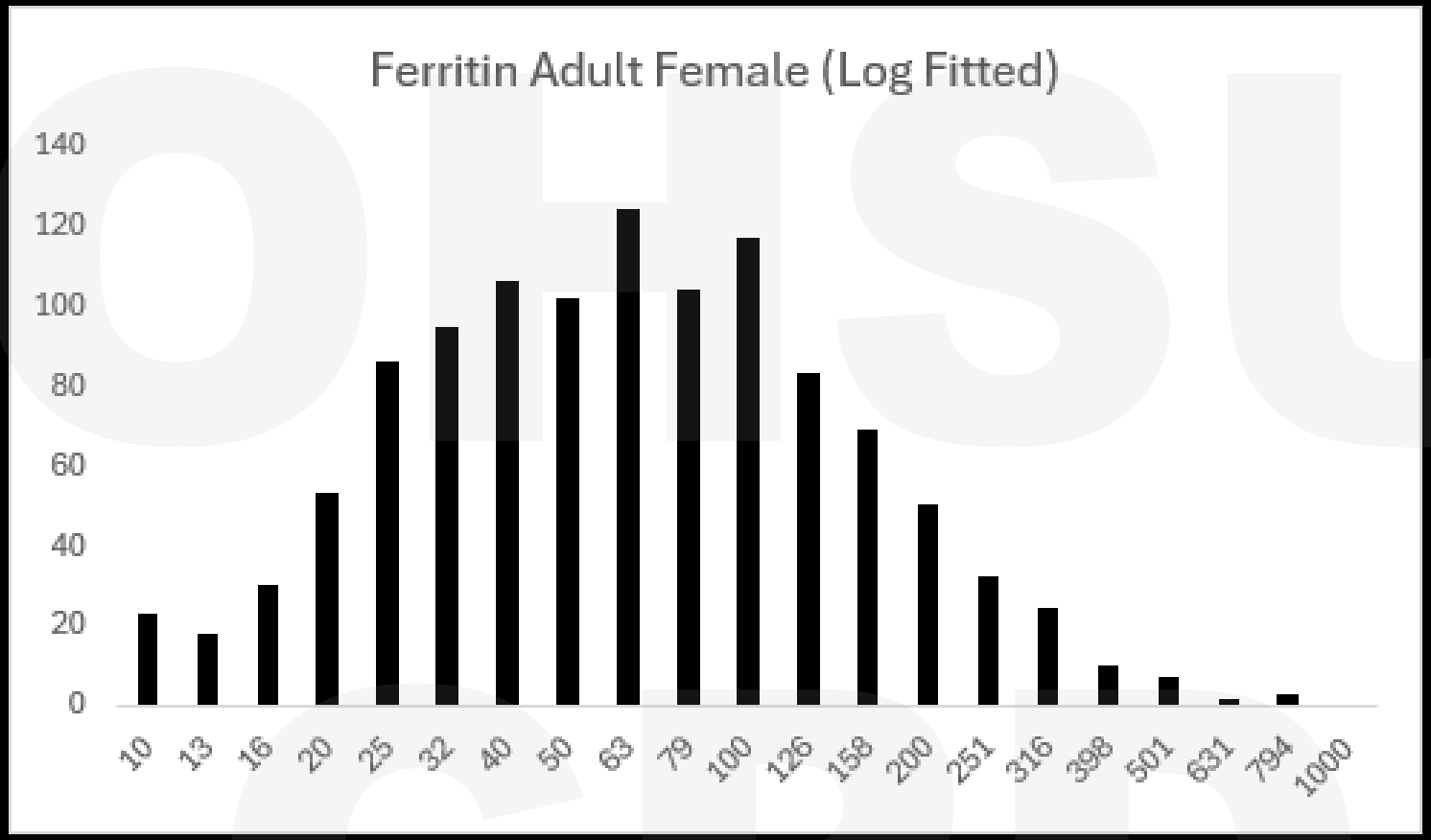
- Ferritin acute phase reactant
- Can be > 1000 ng/dl
- Testing
  - High ferritin
  - High CRP
  - Low iron saturation

Being a Guy

- Ferritins can range up to 4-500 ng/dl



Male Log Fitted	
Mean	86.5
SD	2.3
Low Range	16.3
High Range	457.5



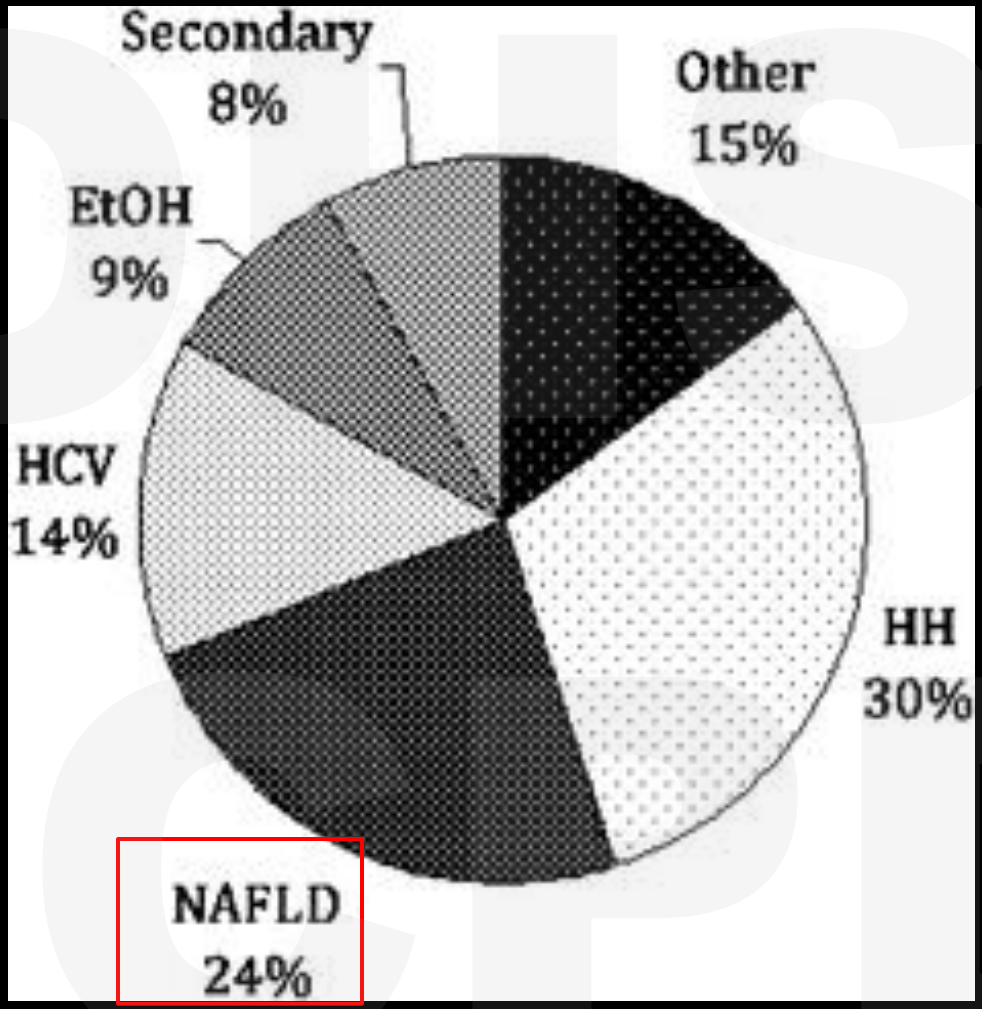
Female Log Fitted	
Mean	55.9
SD	2.4
Low Range	10.0
High Range	312.1

Liver Disease

- Ferritin released from damage hepatocytes
- Acute liver disease
  - Very high levels
- Chronic liver disease
  - Up if liver function test up

MASLD

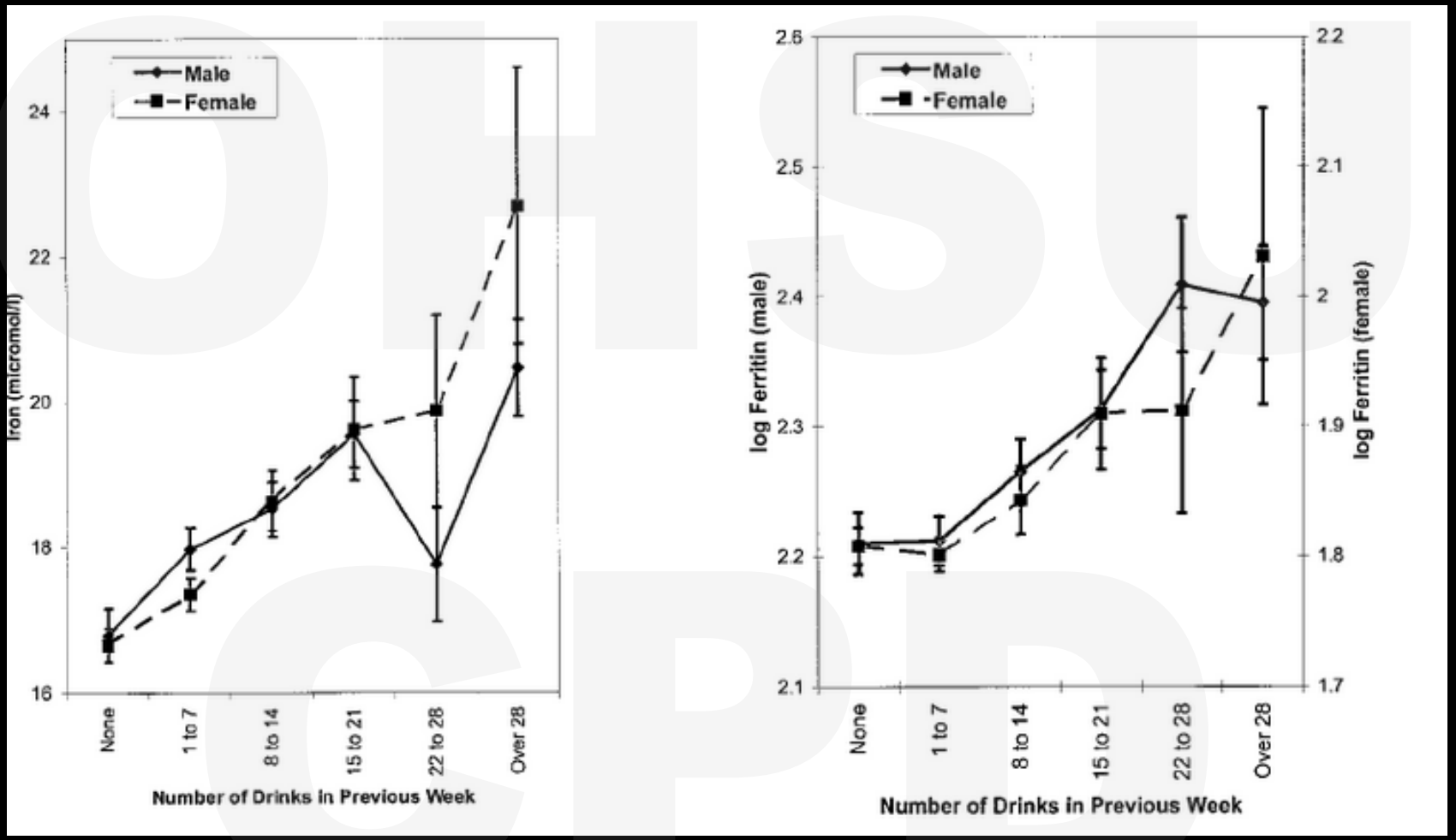
- Common in
  - Diabetes
  - Obesity
- High ferritins
  - Usually normal to low saturations
  - Prognostic indicator
- Phlebotomy not helpful



Dever JB, Digestive Diseases and Sciences, Dig Dis Sci. 2010 Mar;55(3):803-7.

Alcohol

- Significant alcohol use can raise ferritin
  - Liver toxicity?
  - Increase iron absorption
- Can be seen with > 2 drinks/day
  - > 2 beers, > 10 oz wine, > 3 oz hard stuff

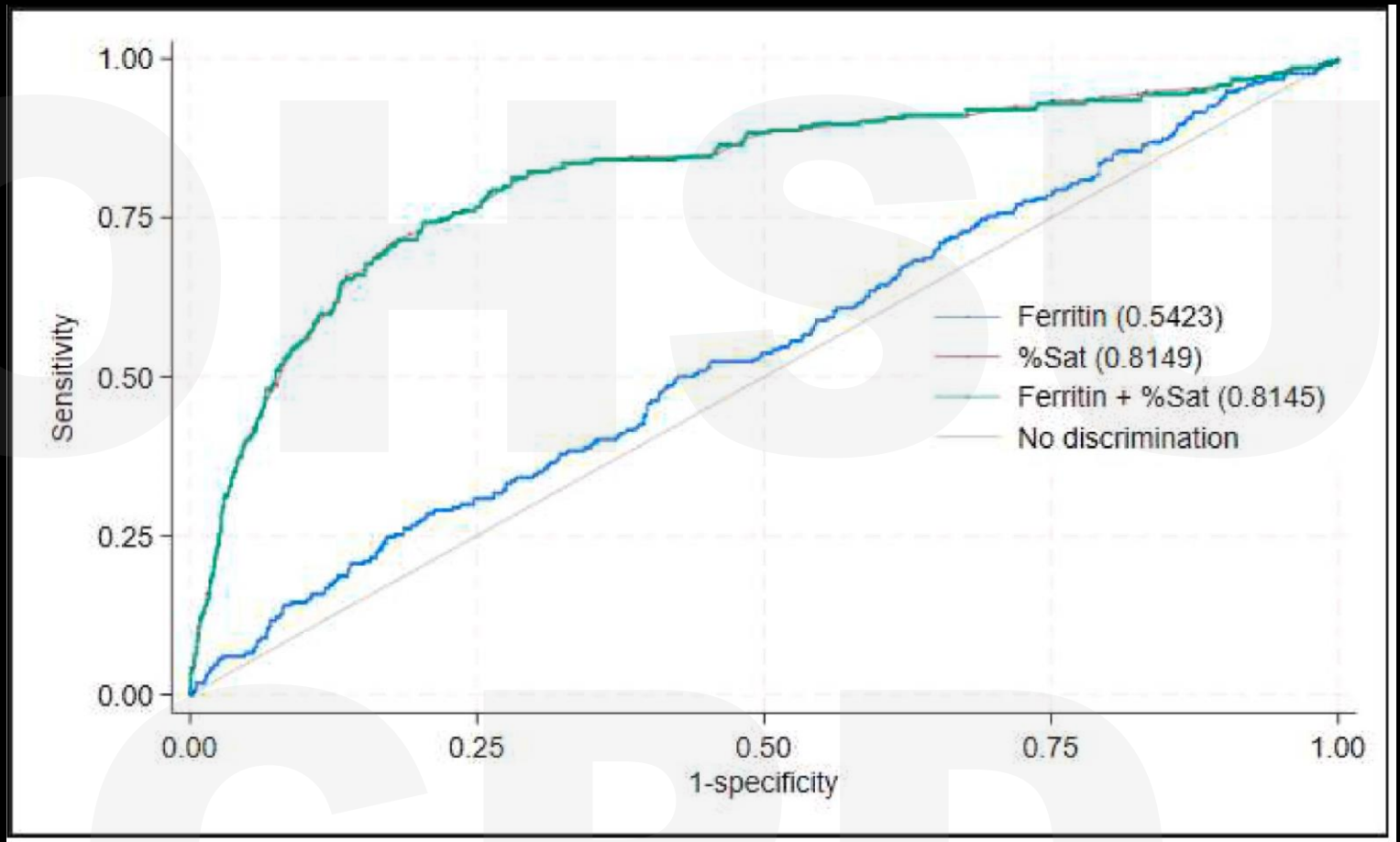


Alcohol Clin Exp Res. 2001 Jul;25(7):1037-45.


OHSU

Work Up of High Ferritins

- First line
  - Saturation
    - > 50% -worrisome for iron overload
    - < 20% - inflammation
- CMP
- Alcohol history
- Hbg A1C
- Reticulocyte count



	ROC area (AUC)	95% conf. interval
Ferritin	0.54	0.50, 0.58
TSat	0.82	0.78, 0.85
Ferritin + TSat	0.82	0.80, 0.85

Clin Biochem. 2025 Jan;135:110860.

Pathway

- High ferritin
- Check Sat
- >45% - check HFE genotype
- Ferritin > 800 – measure iron stores

Genetic Hemochromatosis

- At 4 kinds of defects
- Types 1 and 4 more common
- Mutations much more common than disease

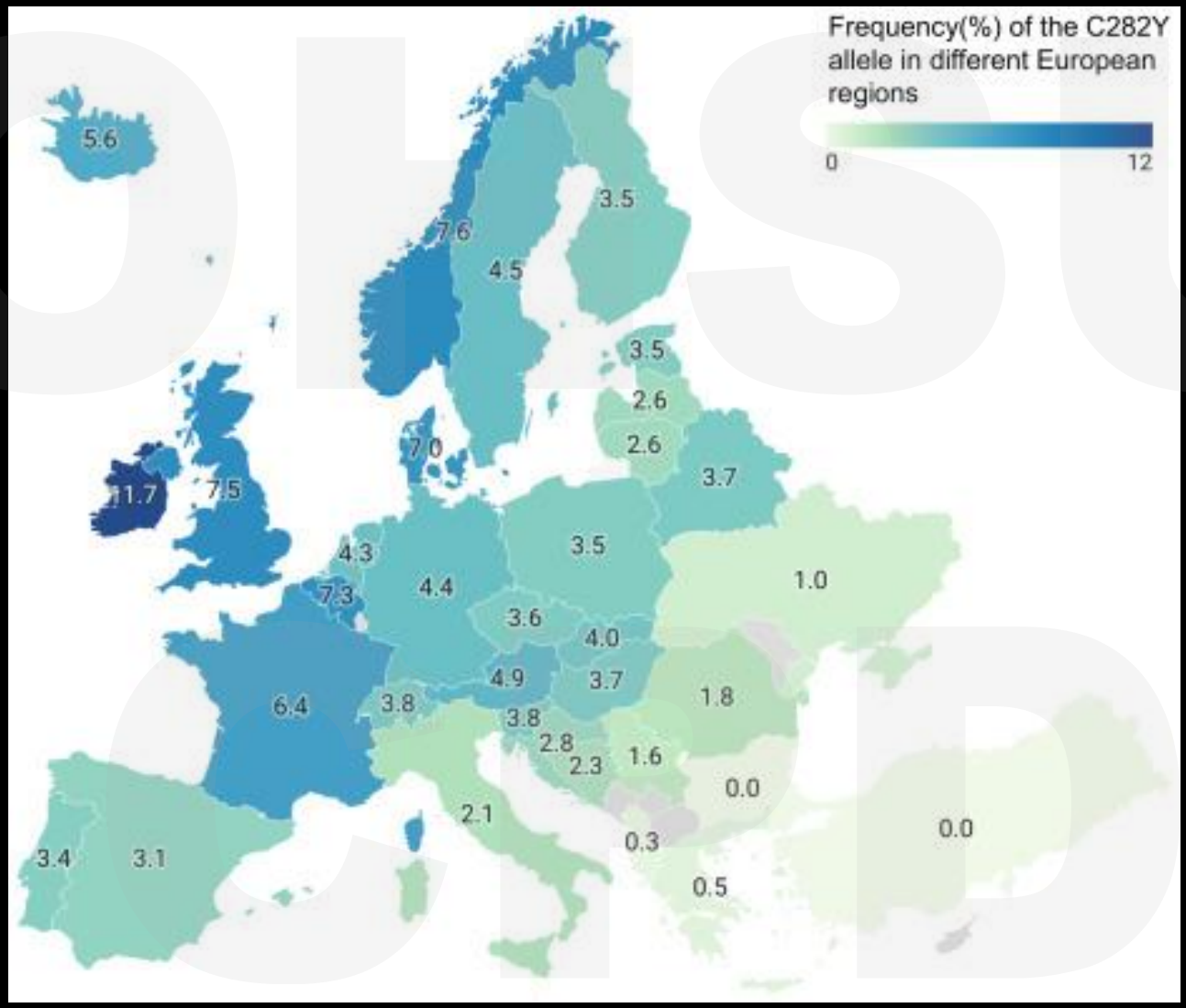
HH Type 1

- Autosomal Recessive
- Carrier frequency - 1 in 10
- Homozygotes ~ 1 in 200 Caucasians
  - 1-21% symptomatic
- Clinical manifestation
  - 5:1 males:females
  - Late onset - > 40 years
  - Defects in HFE gene
  - Liver, joints, endocrine

Genetics

- Classic C282Y homozygous
  - Men ~ 20% penetrance
  - Women ~ 1%
- H63D
  - Not a true mutation and testing no longer recommended

- Blood Red Cells & Iron (2026) 2 (1): 100034.


Frequency(%) of the C282Y allele in different European regions
0
12
5.6
7.6
4.5
3.5
3.5
2.6
2.6
3.7
7.0
11.7
7.5
4.3
7.3
4.4
3.5
1.0
3.6
4.0
4.9
3.7
1.8
6.4
3.8
3.8
2.8
2.3
1.6
0.0
2.1
0.3
0.0
3.4
3.1
0.5

Hemochromatosis NOS

- ~ 20% negative HFE
  - High ferritin
  - Tissue iron overload
- Phlebotomy

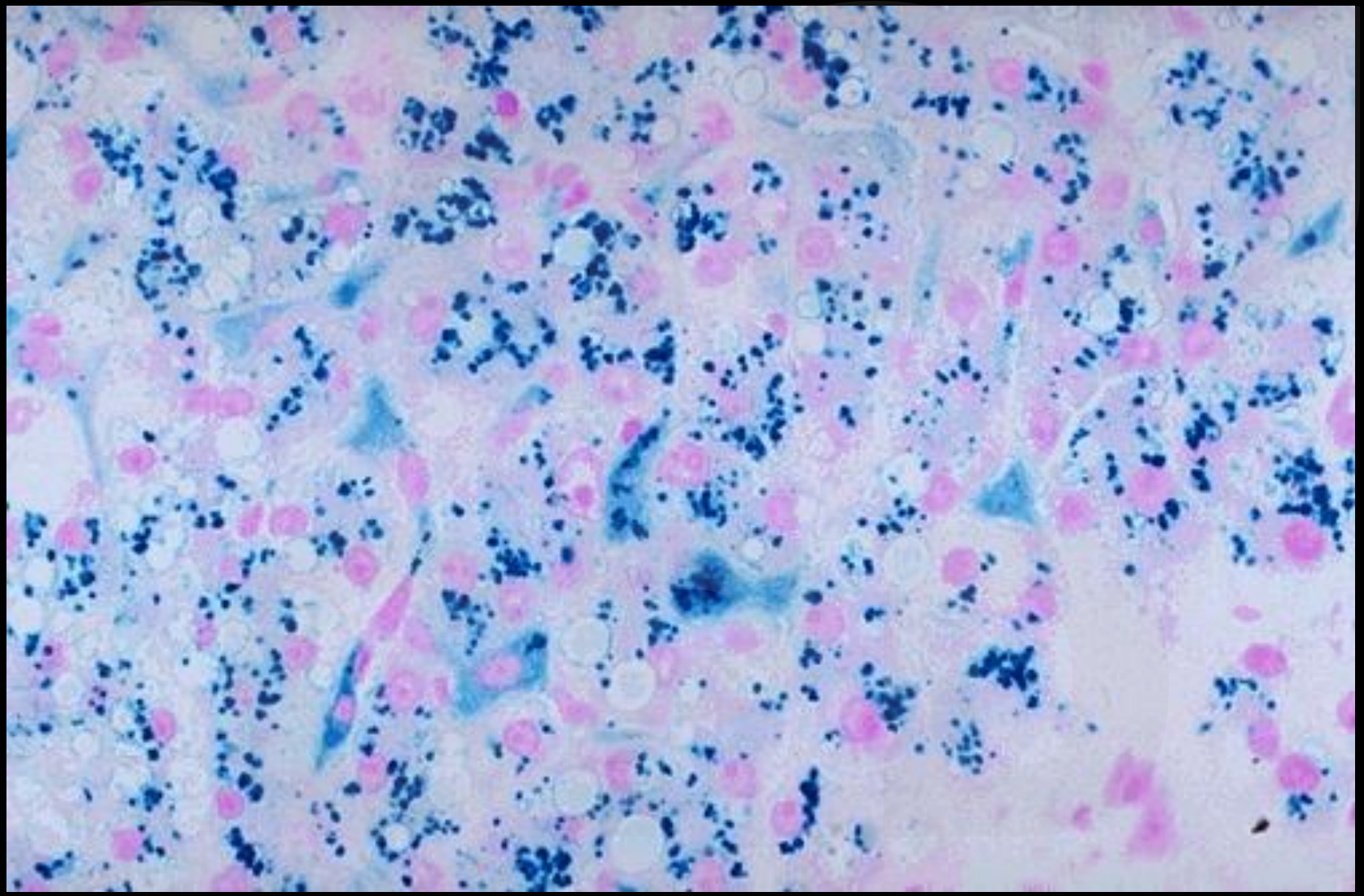
How to Measure Iron

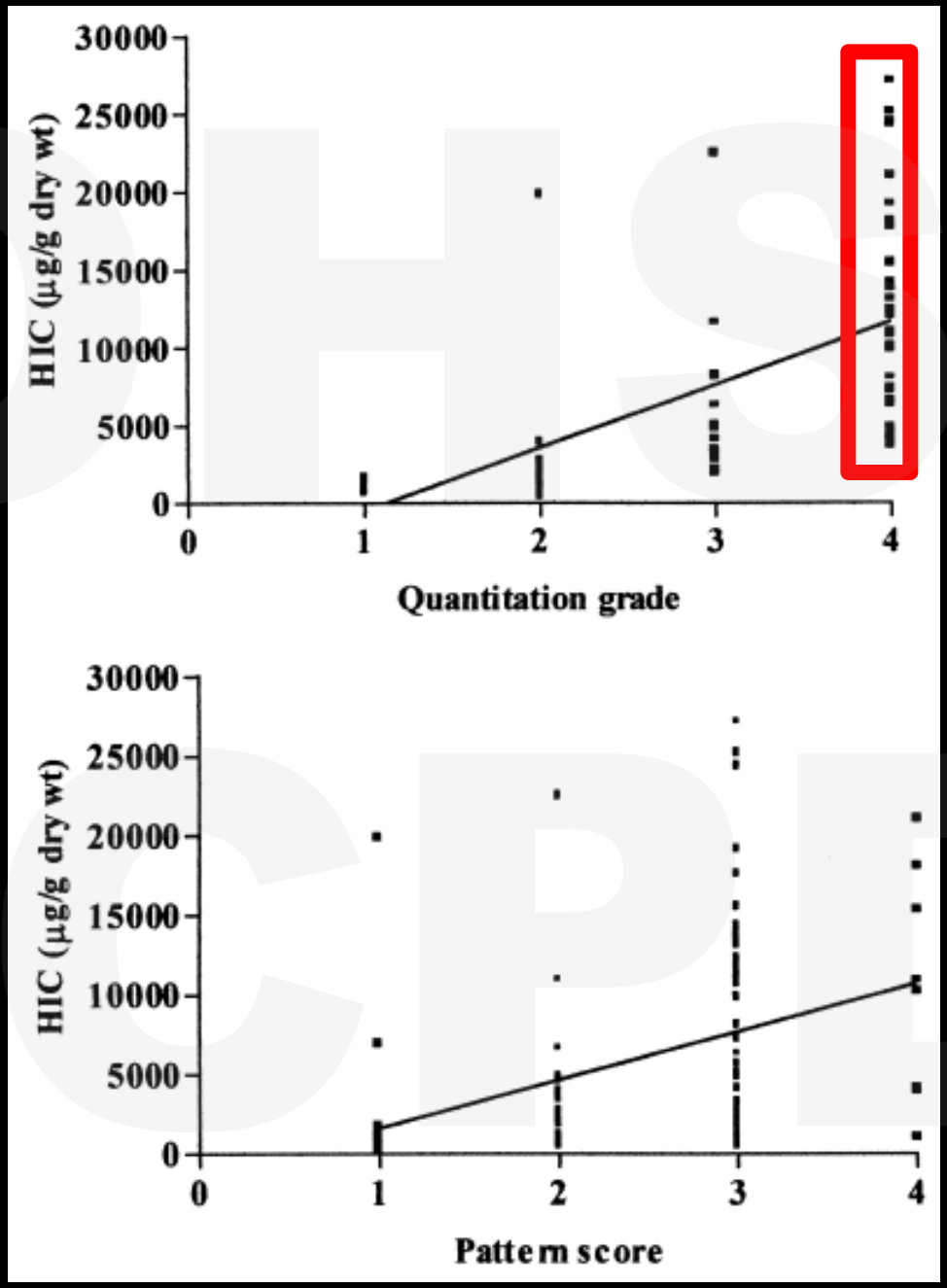
Ferritin

- Great for iron deficiency
- High levels worrisome for iron overload
- No relationship with high iron and amount of tissue iron

Biopsy

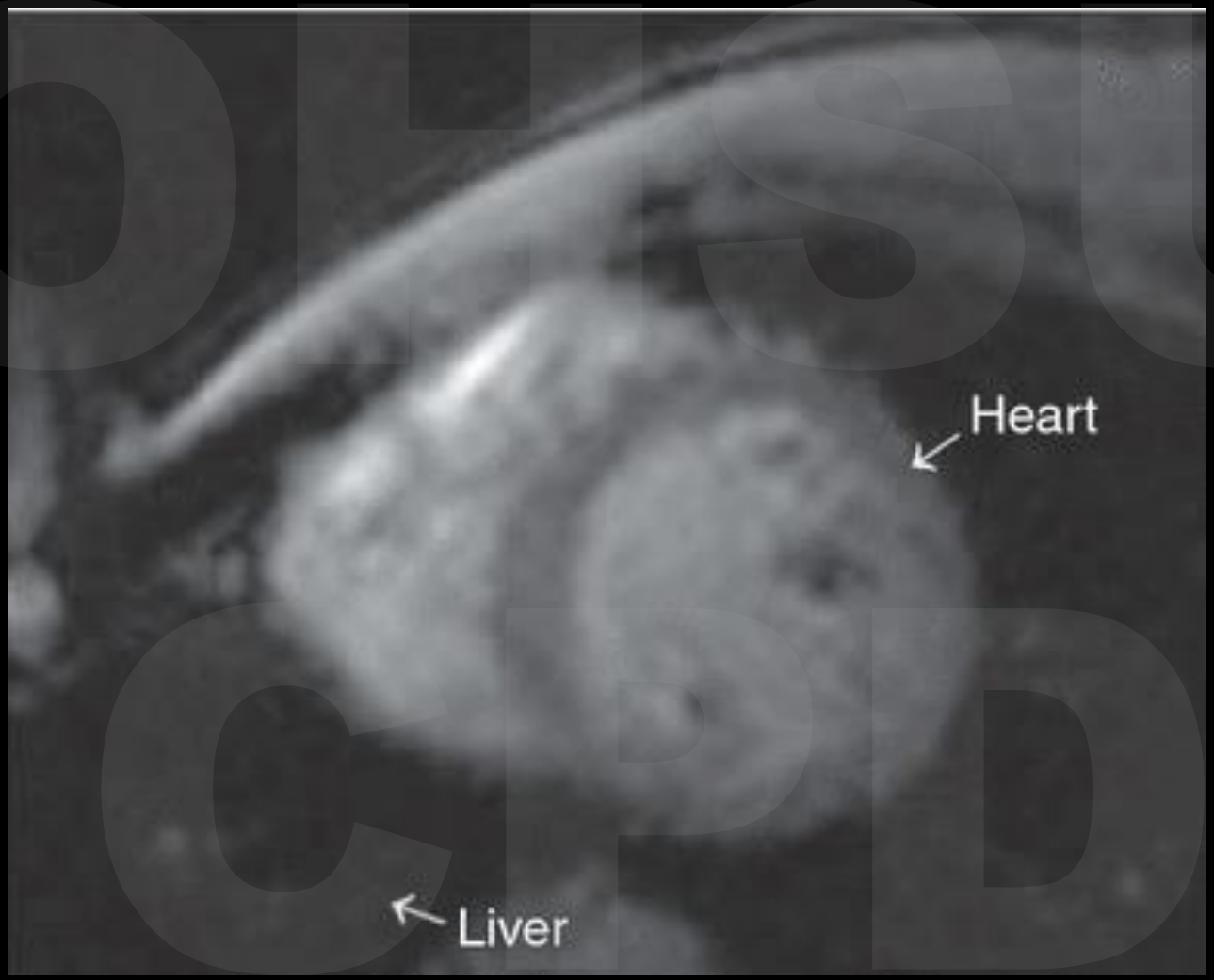
- Liver
  - Iron stain – quantitative
  - Tissue iron concentration key
- Cardiac – biopsy
- Marrow biopsy
  - Not helpful
    - Low in hemochromatosis!

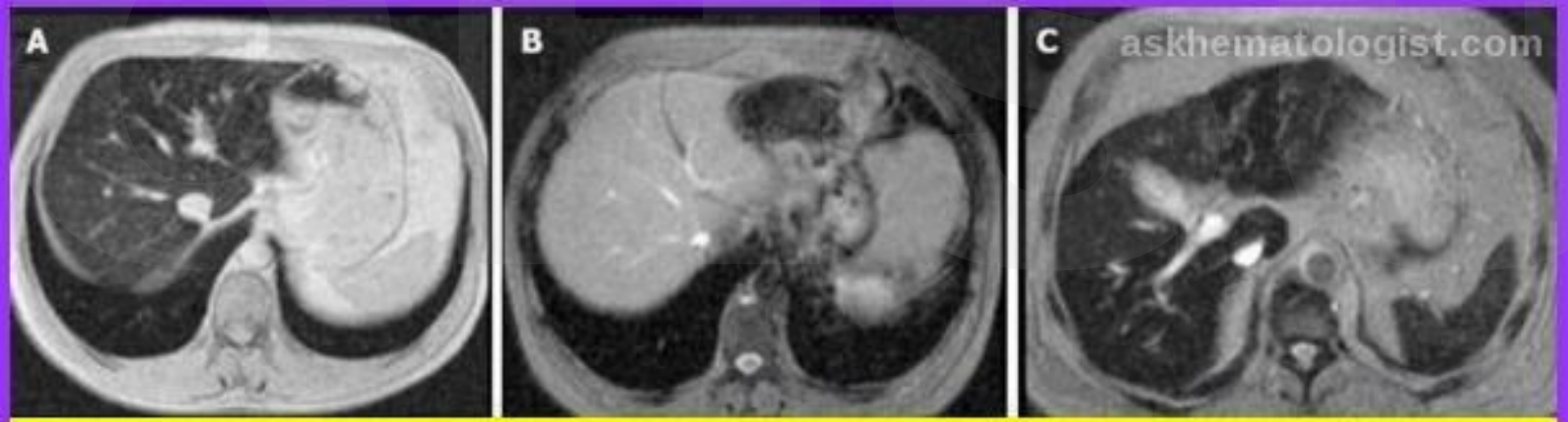



HIC (µg/g dry wt)
30000
25000
20000
15000
10000
5000
0
0
1
2
3
4
Quantitation grade
HIC (µg/g dry wt)
30000
25000
20000
15000
10000
5000
0
0
1
2
3
4
Pattern score

MRI

- Liver
  - Correlation with T2* scan and iron load
  - Now the go-to test
- Cardiac MRI
  - Rapidly becoming gold standard


Heart
Liver



Liver MRI Scan - Iron Overload

A: Hereditary hemochromatosis-Important reduction in signal intensity from the liver.

B: Prolonged treatment with phlebotomies. Liver signal intensity is normal.

C: Secondary hemochromatosis. Reduction in signal intensity in the liver and the spleen.

Therapy

- Inflammation
  - Primary cause
- Steatohepatitis
  - Lipid and diabetes control
  - No benefit phlebotomy
- Alcohol
  - Decrease drinking
- Iron overload
  - Phlebotomy

Therapy: Hemochromatosis

- Phlebotomy
  - Weekly in symptomatic patients
  - Weekly to biweekly in carriers if ferritin > 300
- Goals
  - Ferritins < 50 (higher if older)
- Iron overload in congenital anemias
  - Phlebotomy if tolerated

Goals of Therapy

- No end organ damage
  - Full life expectancy
- Liver cirrhosis
  - Minimal improvement
  - Screen for hepatoma

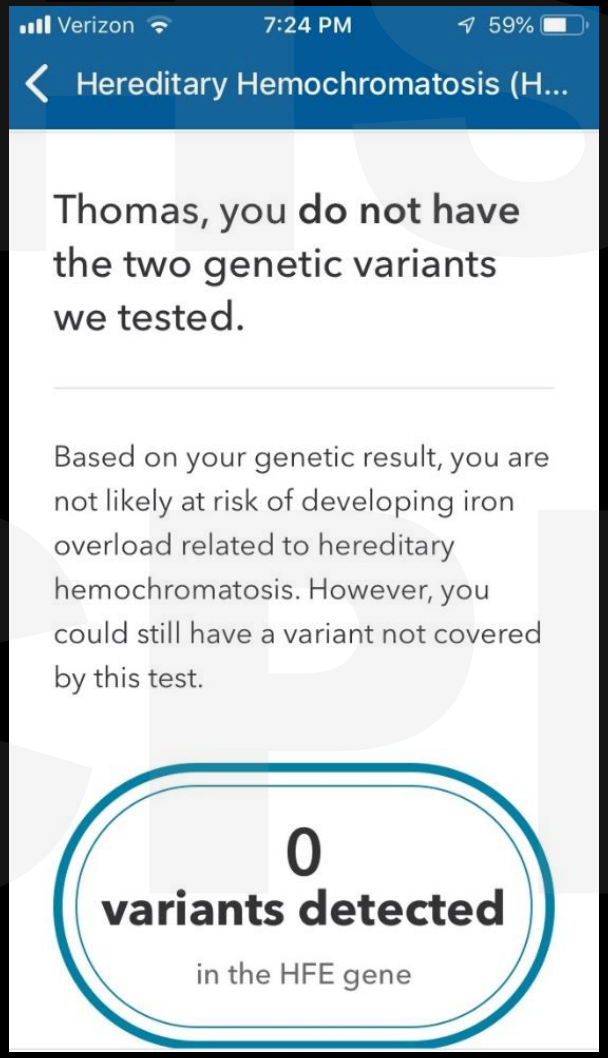
Goals of Therapy

- Cardiac
  - Reversal
- Diabetes
  - Some improvement
- Joints
  - Usually no improvement

Erythrocytosis

- Carries of HFE mutations can have erythrocytosis
  - Not due to higher iron levels
- Both homozygous and heterozygous
- HFE mutations overrepresented in athletes

23&Me


Verizon
7:24 PM
59%
Hereditary Hemochromatosis (H...
Thomas, you do not have the two genetic variants we tested.
Based on your genetic result, you are not likely at risk of developing iron overload related to hereditary hemochromatosis. However, you could still have a variant not covered by this test.
0
variants detected
in the HFE gene

Work-Up

- Repeat genetics
- Ferritin
  - > 300:phlebotomy
  - < 300: yearly ferritins
  - < 50: ok to treat iron deficiency
- Family screening