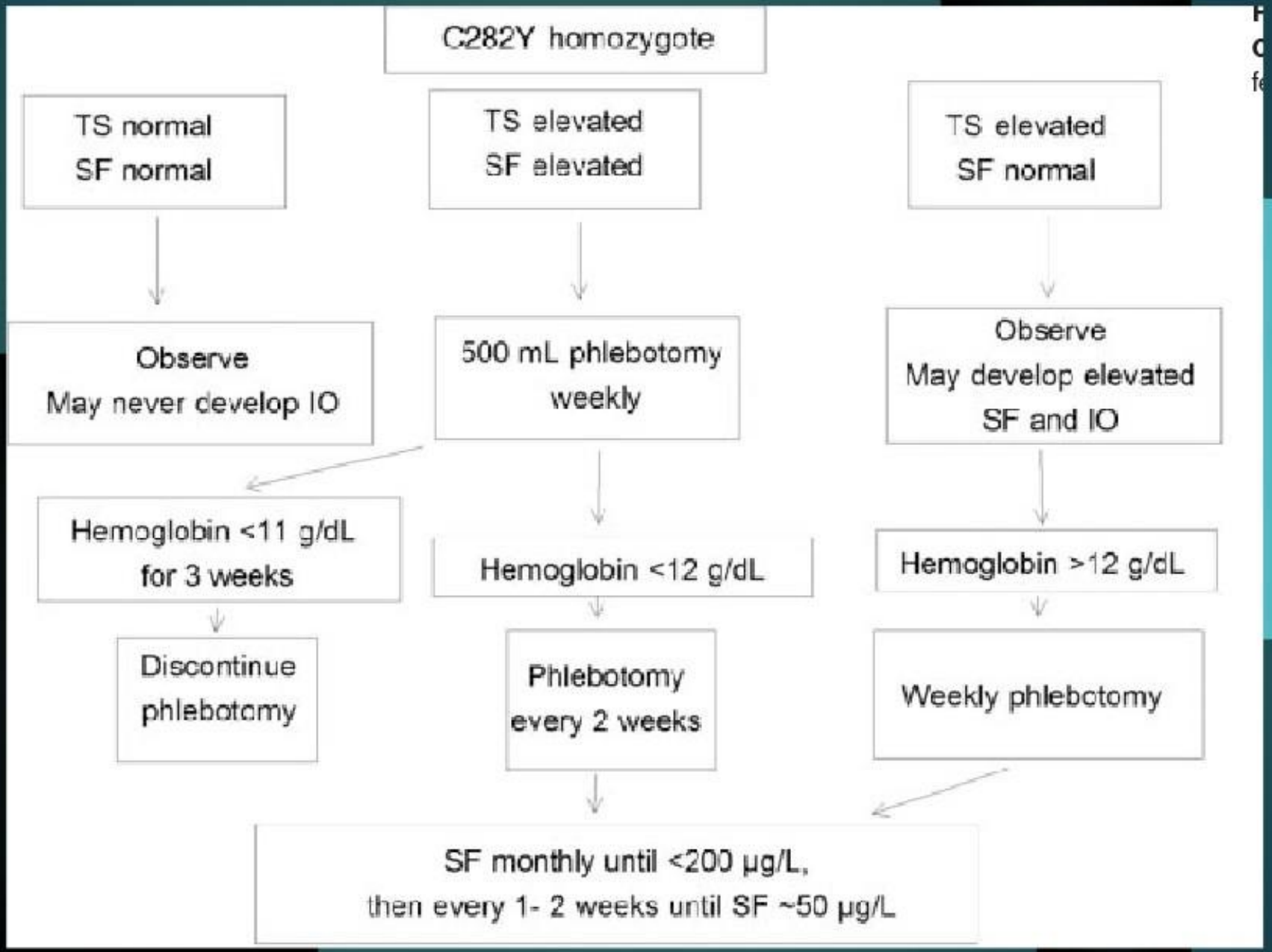
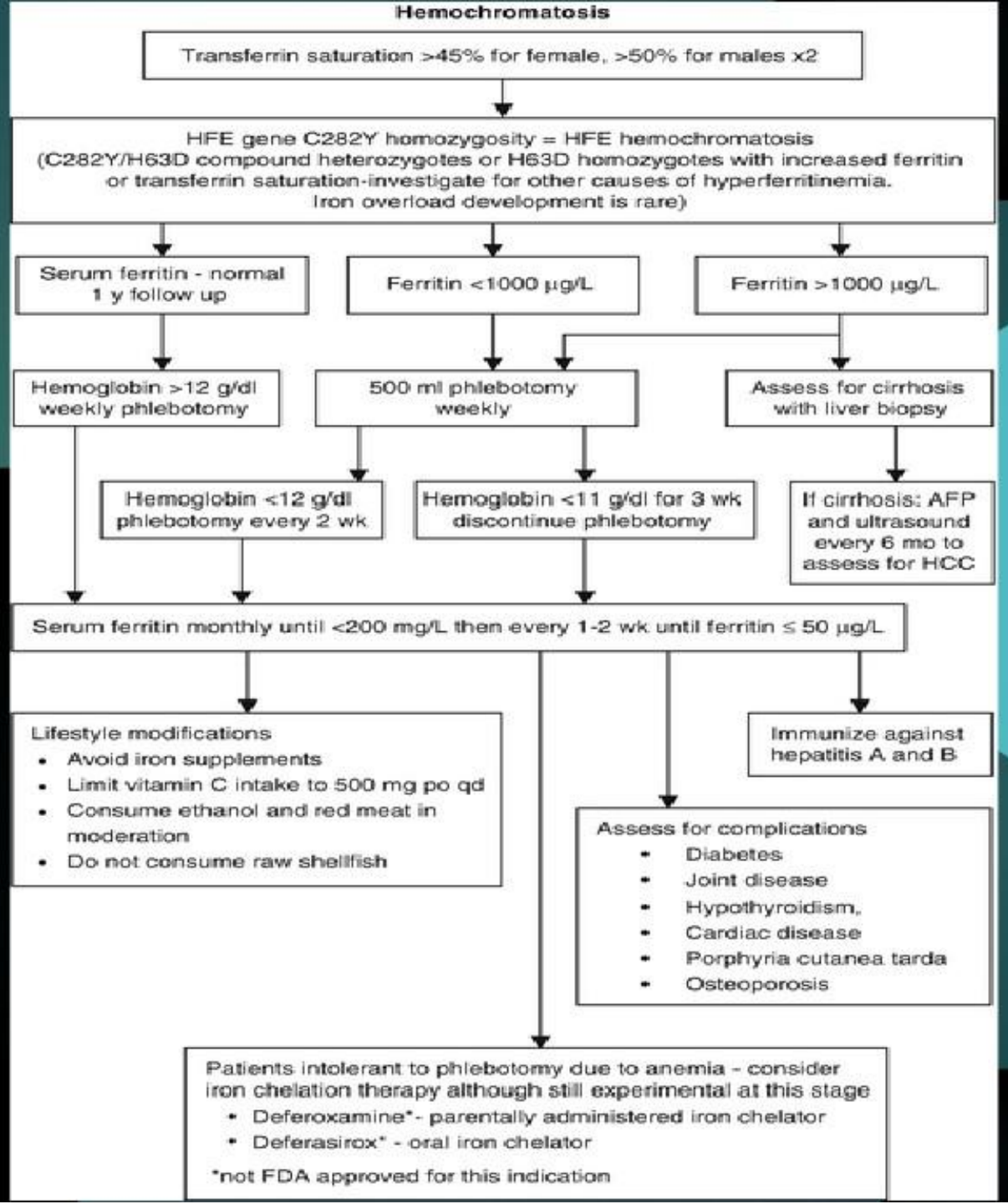
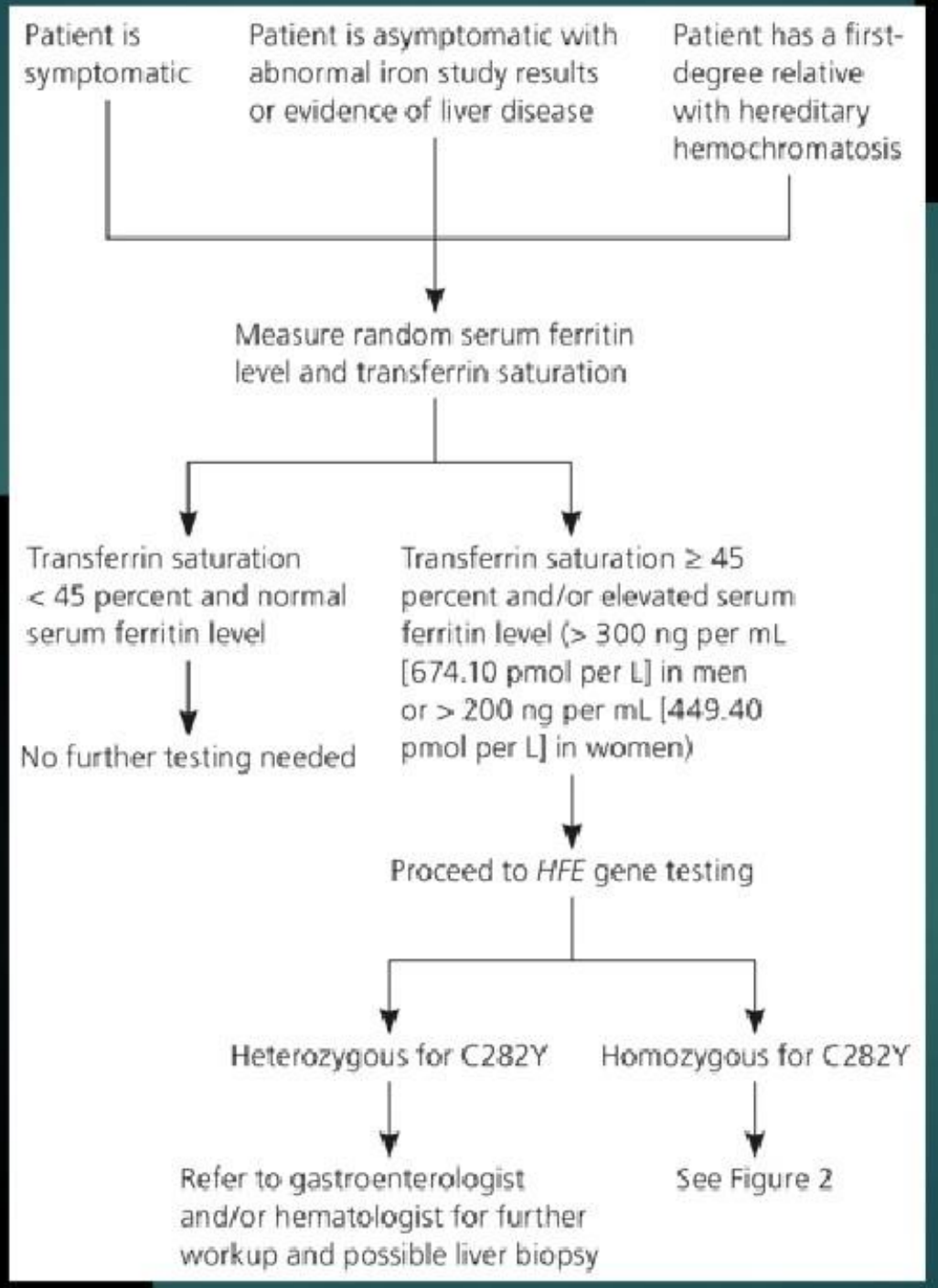
HAEMOCHROMATOSIS

- BY HARI SHANKAR PANDEY

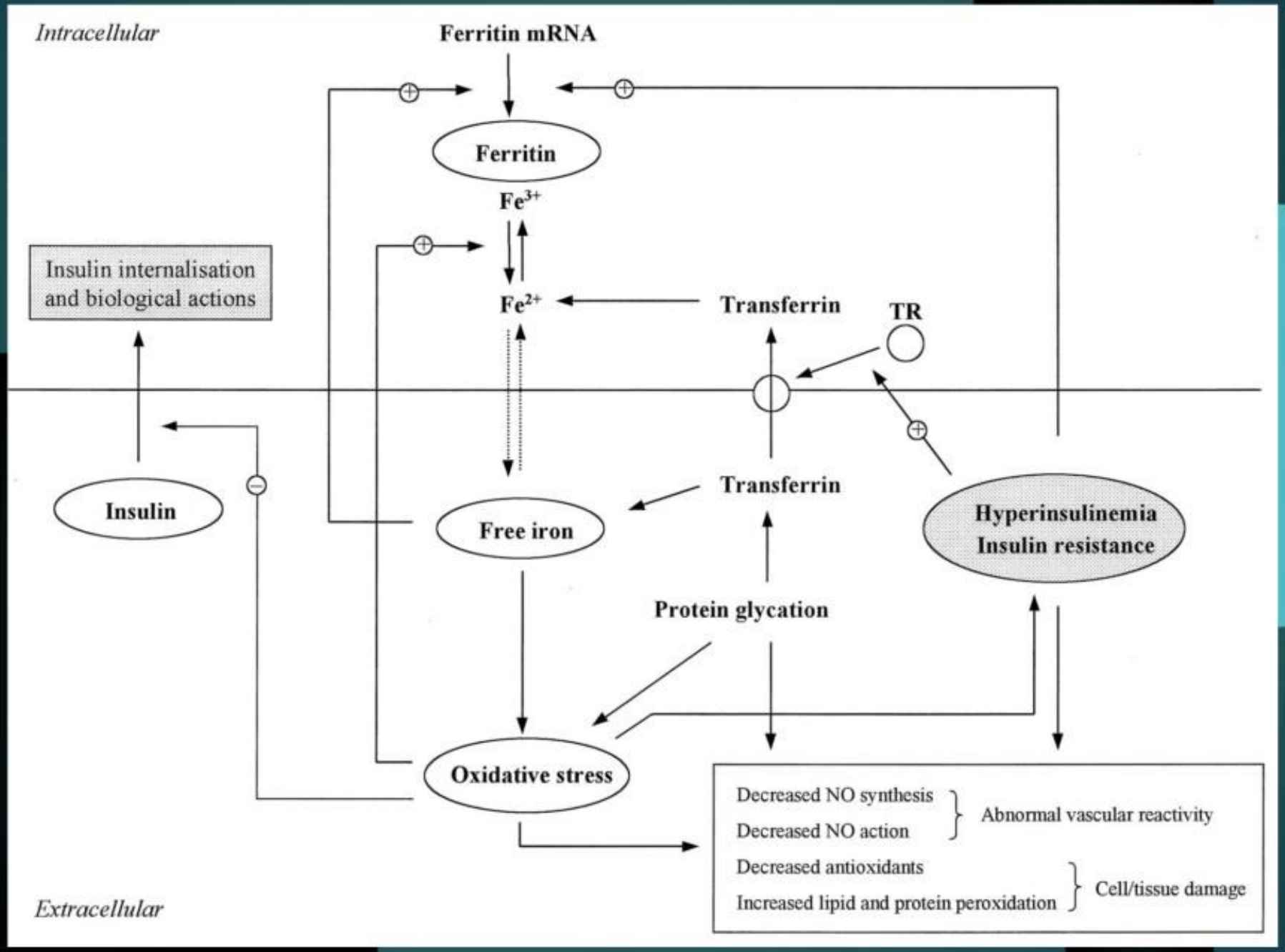

C282Y homozygote
TS normal
SF normal
TS elevated
SF elevated
TS elevated
SF normal
Observe
May never develop IO
500 mL phlebotomy
weekly
Observe
May develop elevated
SF and IO
Hemoglobin <11 g/dL
for 3 weeks
Hemoglobin <12 g/dL
Hemoglobin >12 g/dL
Discontinue
phlebotomy
Phlebotomy
every 2 weeks
Weekly phlebotomy
SF monthly until <200 µg/L,
then every 1- 2 weeks until SF ~50 µg/L

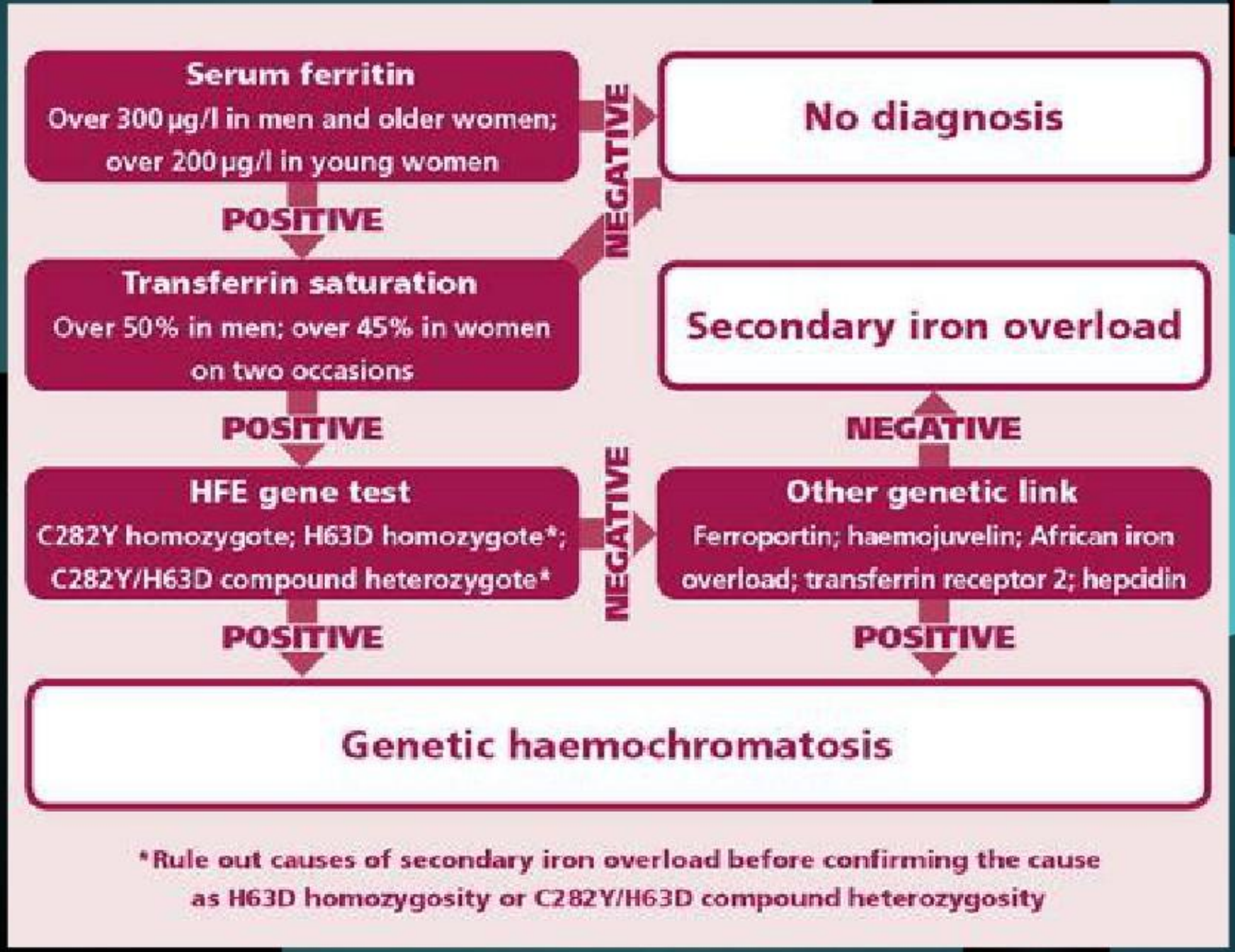

Hemochromatosis
Transferrin saturation >45% for female, >50% for males x2
HFE gene C282Y homozygosity = HFE hemochromatosis
(C282Y/H63D compound heterozygotes or H63D homozygotes with increased ferritin or transferrin saturation-investigate for other causes of hyperferritinemia. Iron overload development is rare)
Serum ferritin - normal 1 y follow up
Ferritin <1000 µg/L
Ferritin >1000 µg/L
Hemoglobin >12 g/dl weekly phlebotomy
500 ml phlebotomy weekly
Assess for cirrhosis with liver biopsy
Hemoglobin <12 g/dl phlebotomy every 2 wk
Hemoglobin <11 g/dl for 3 wk discontinue phlebotomy
If cirrhosis: AFP and ultrasound every 6 mo to assess for HCC
Serum ferritin monthly until <200 mg/L then every 1-2 wk until ferritin ≤ 50 µg/L
Lifestyle modifications
Avoid iron supplements
Limit vitamin C intake to 500 mg po qd
Consume ethanol and red meat in moderation
Do not consume raw shellfish
Immunize against hepatitis A and B
Assess for complications
Diabetes
Joint disease
Hypothyroidism,
Cardiac disease
Porphyria cutanea tarda
Osteoporosis
Patients intolerant to phlebotomy due to anemia - consider iron chelation therapy although still experimental at this stage
Deferoxamine*- parentally administered iron chelator
Deferasirox* - oral iron chelator
*not FDA approved for this indication


Patient is symptomatic
Patient is asymptomatic with abnormal iron study results or evidence of liver disease
Patient has a first-degree relative with hereditary hemochromatosis
Measure random serum ferritin level and transferrin saturation
Transferrin saturation < 45 percent and normal serum ferritin level
No further testing needed
Transferrin saturation ≥ 45 percent and/or elevated serum ferritin level (> 300 ng per mL [674.10 pmol per L] in men or > 200 ng per mL [449.40 pmol per L] in women)
Proceed to HFE gene testing
Heterozygous for C282Y
Homozygous for C282Y
Refer to gastroenterologist and/or hematologist for further workup and possible liver biopsy
See Figure 2

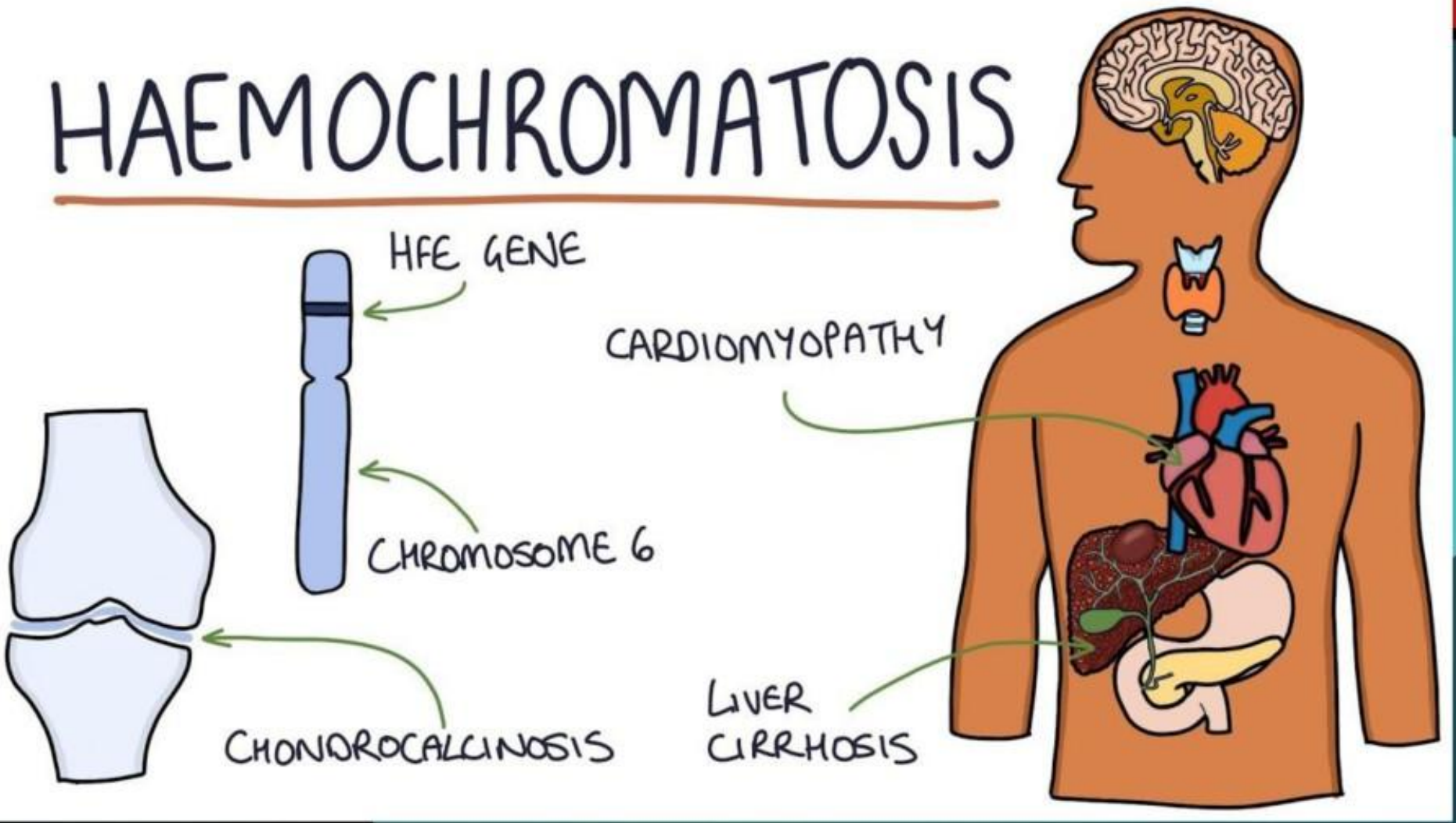
Hemochromatosis Overview

- History
  - Classic triad described in the 1865 by Trousseau
    - Diabetes, bronze skin, cirrhosis
  - Named “Hemochromatosis” in 1889 by Von Recklinghaussen
    - Iron storage and widespread tissue injury
  - Inheritance described in 1935
  - HLA linkage to chromosome 6 identified 1976


Intracellular
Ferritin mRNA
Ferritin
Fe3+
Insulin internalisation and biological actions
Fe2+
Transferrin
TR
Insulin
Free iron
Transferrin
Hyperinsulinemia
Insulin resistance
Protein glycation
Oxidative stress
Decreased NO synthesis
Decreased NO action
Abnormal vascular reactivity
Decreased antioxidants
Increased lipid and protein peroxidation
Cell/tissue damage
Extracellular

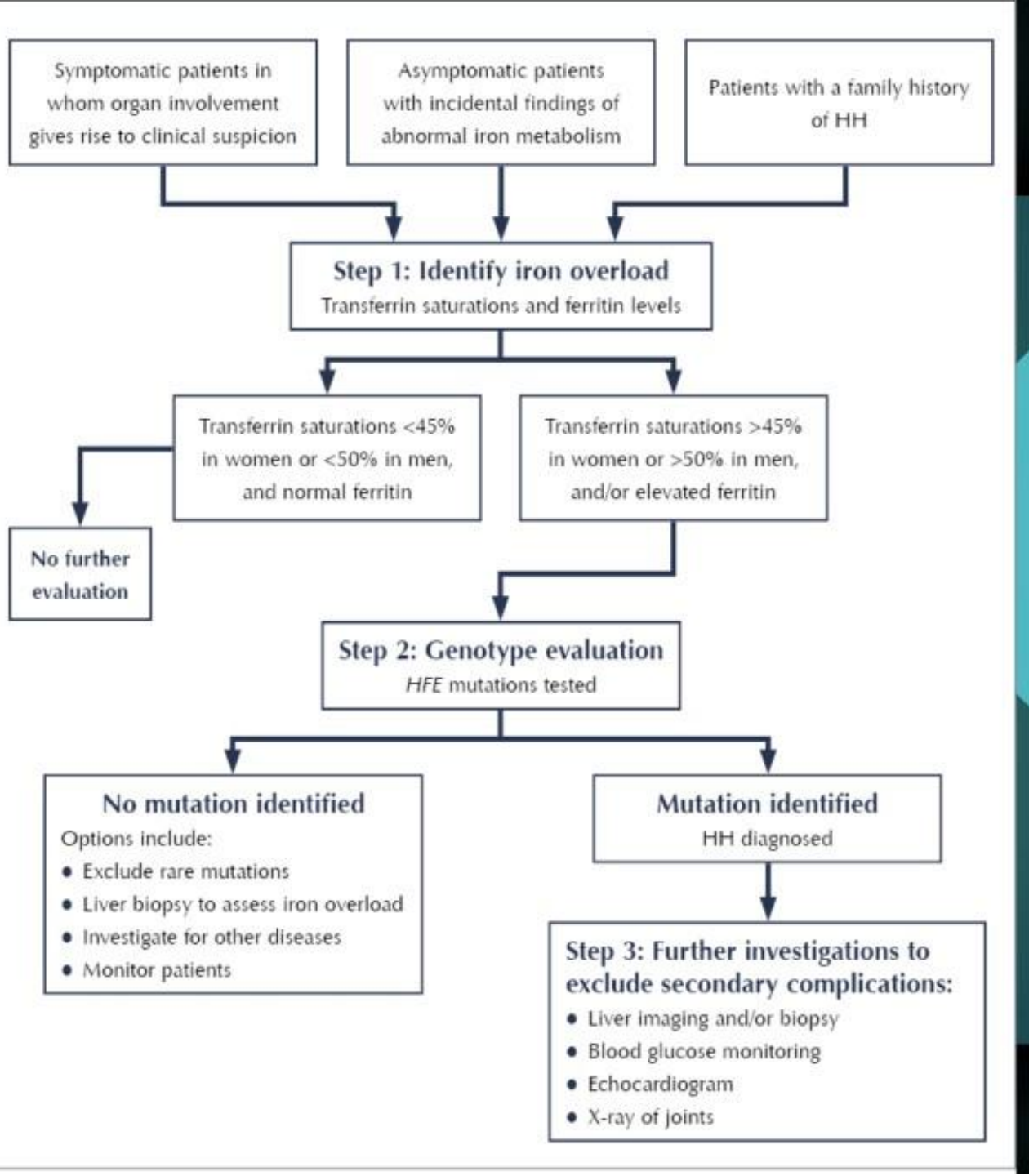

Serum ferritin
Over 300 µg/l in men and older women; over 200 µg/l in young women
NEGATIVE
No diagnosis
POSITIVE
Transferrin saturation
Over 50% in men; over 45% in women on two occasions
NEGATIVE
Secondary iron overload
POSITIVE
NEGATIVE
HFE gene test
C282Y homozygote; H63D homozygote*; C282Y/H63D compound heterozygote*
NEGATIVE
Other genetic link
Ferroportin; haemojuvelin; African iron overload; transferrin receptor 2; hepcidin
POSITIVE
POSITIVE
Genetic haemochromatosis
*Rule out causes of secondary iron overload before confirming the cause as H63D homozygosity or C282Y/H63D compound heterozygosity

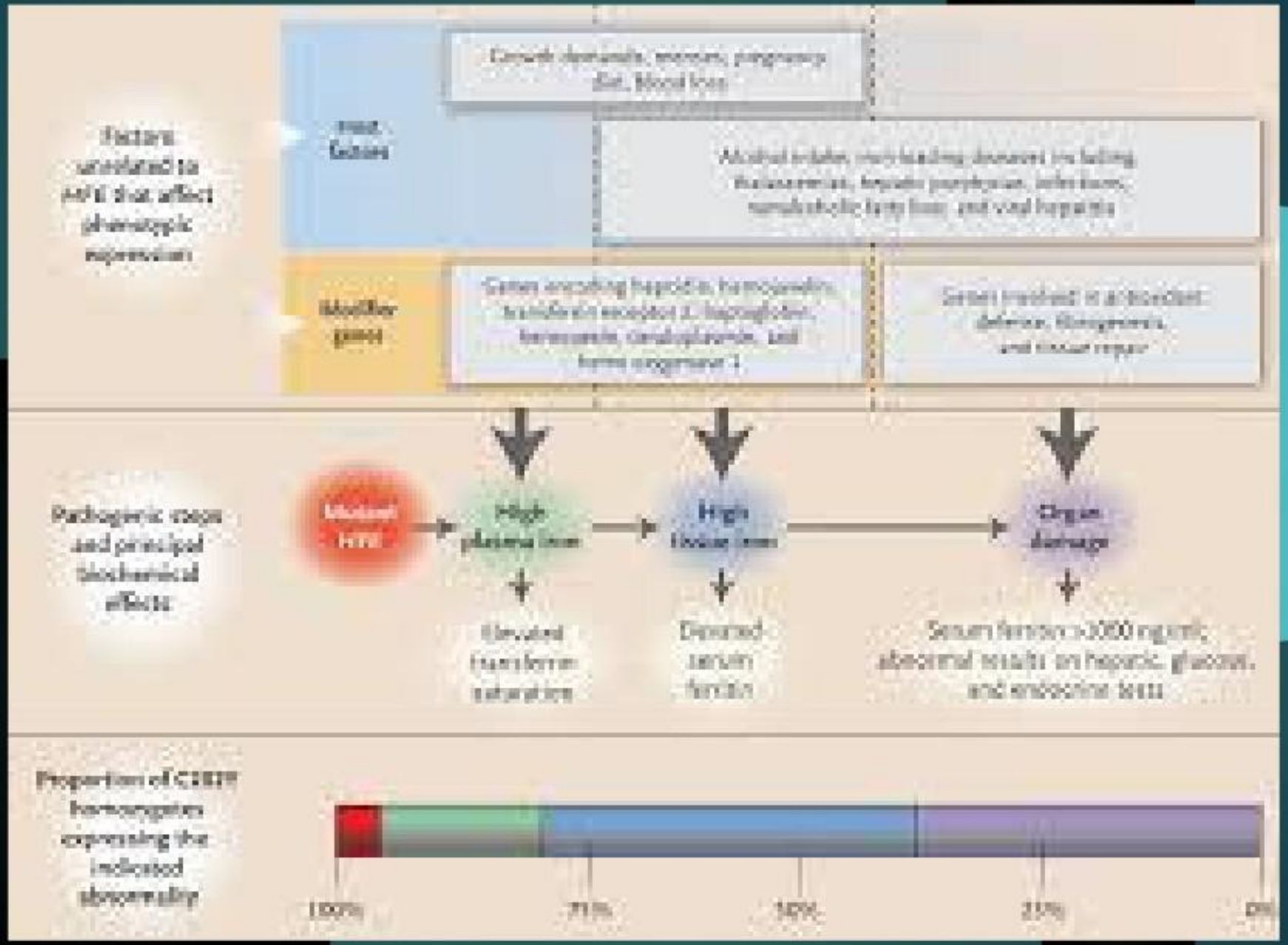
HAEMOCHROMATOSIS



Iron Overload or Hemochromatosis treatment

- The most common way to treat iron overload is to reduce the amount of iron in the body. This can be done through diet by eating foods low in iron or through the withdrawal of blood. The preferred treatment for reducing iron levels in hemochromatosis patients is called **therapeutic phlebotomy (repeated venesection)**.


Symptomatic patients in whom organ involvement gives rise to clinical suspicion
Asymptomatic patients with incidental findings of abnormal iron metabolism
Patients with a family history of HH
Step 1: Identify iron overload
Transferrin saturations and ferritin levels
Transferrin saturations <45% in women or <50% in men, and normal ferritin
Transferrin saturations >45% in women or >50% in men, and/or elevated ferritin
No further evaluation
Step 2: Genotype evaluation
HFE mutations tested
No mutation identified
Options include:
• Exclude rare mutations
• Liver biopsy to assess iron overload
• Investigate for other diseases
• Monitor patients
Mutation identified
HH diagnosed
Step 3: Further investigations to exclude secondary complications:
• Liver imaging and/or biopsy
• Blood glucose monitoring
• Echocardiogram
• X-ray of joints


Factors unrelated to HFE that affect phenotypic expression
Host factors
Modifier genes
Pathogenic steps and principal biochemical effects
High plasma iron
High tissue iron
Organ damage
Elevated transferrin saturation
Elevated serum ferritin
Proportion of C282Y homozygotes expressing the indicated abnormality
100%
75%
50%
25%
0%

HFE hemochromatosis

- Caucasian, male, 40–50 years old
- Fatigue, dark skin, arthralgia and/or hepatomegaly
- Elevated TS and SF

TfR2 hemochromatosis

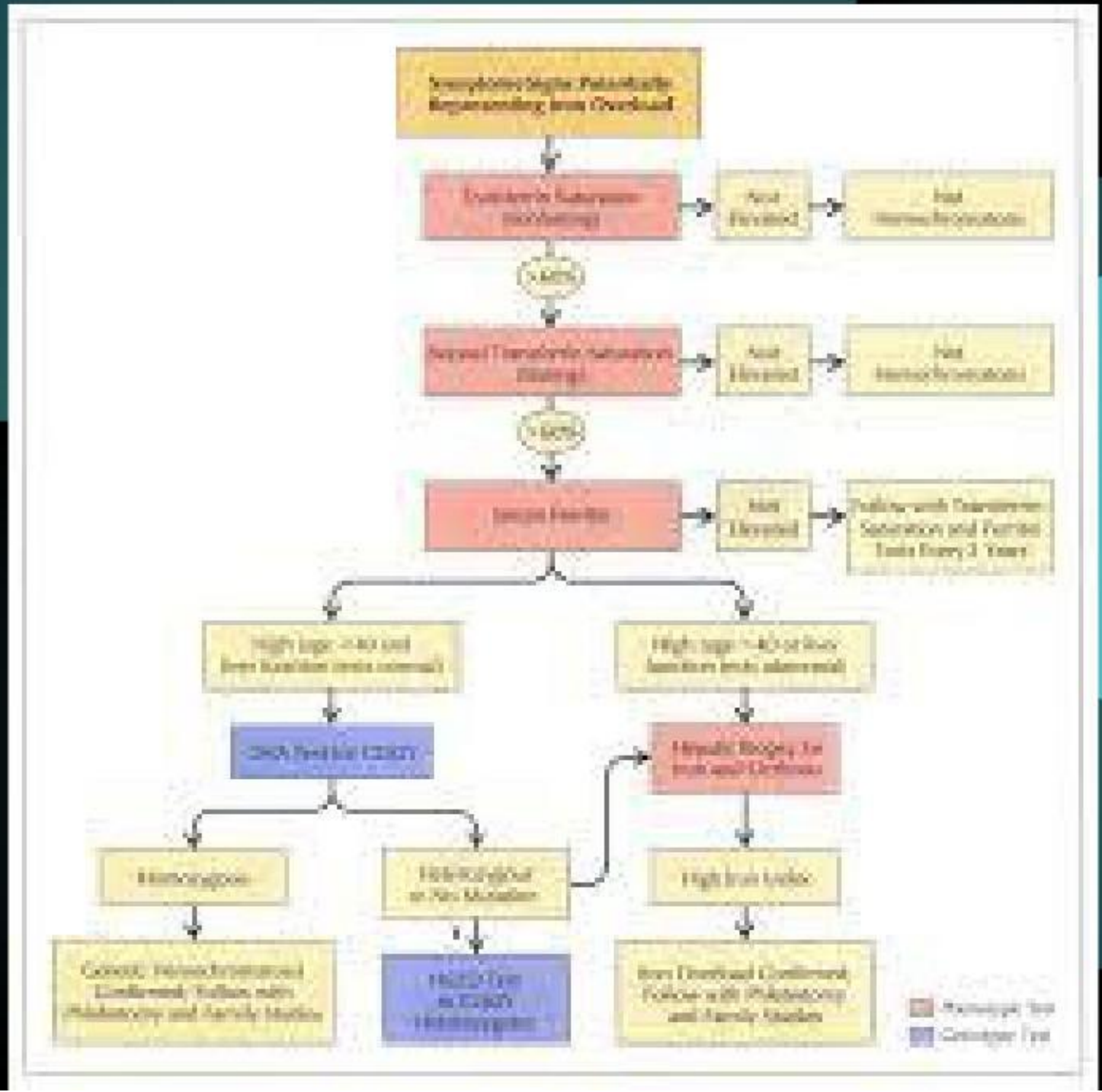
- Caucasian or non-Caucasian, male or female, 30–40 years old
- Cardiomyopathy, endocrinopathy, liver disease
- Elevated TS and SF

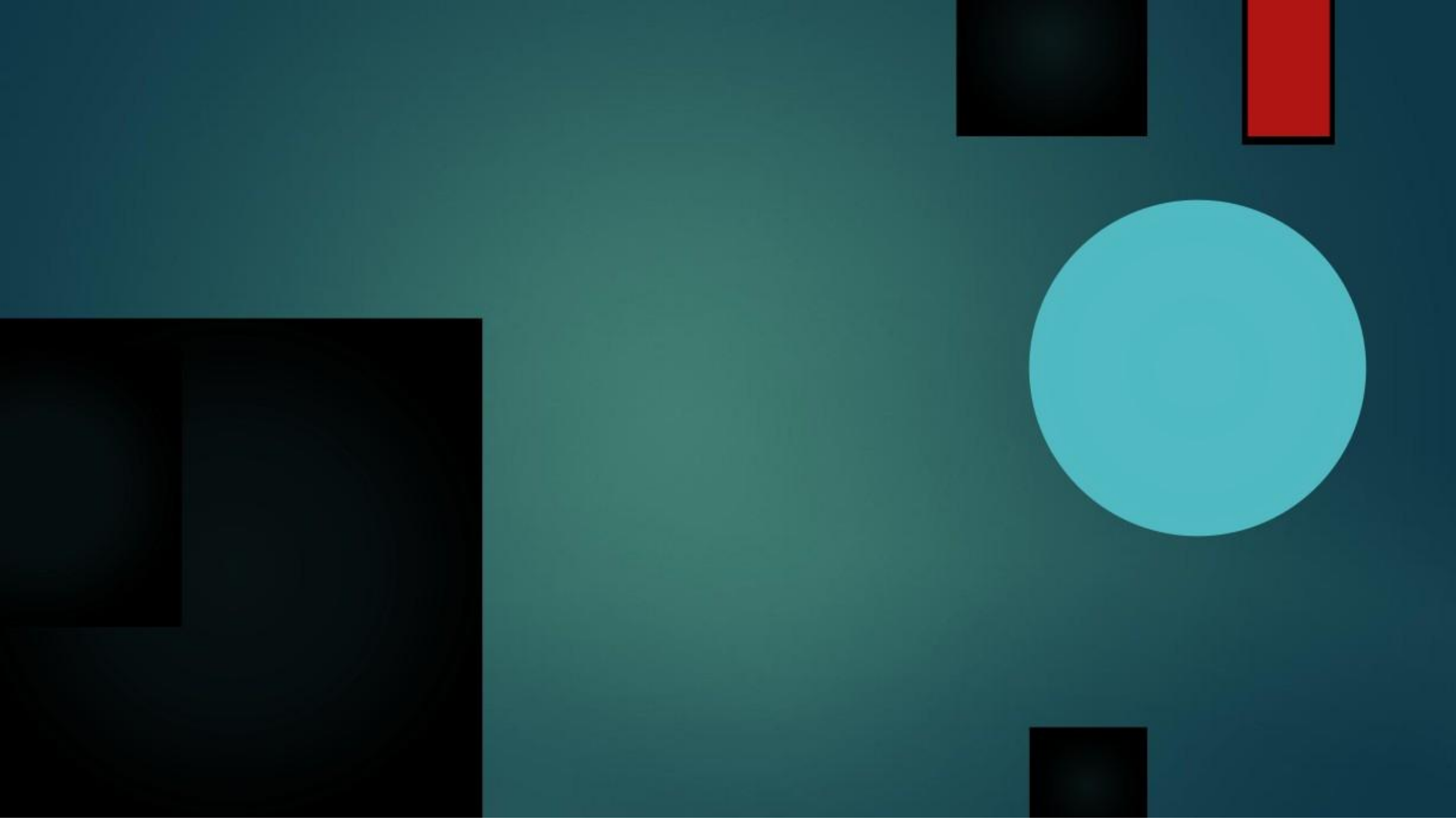
HJV or HAMP hemochromatosis

- Caucasian or non-Caucasian, male or female, 15–20 years old
- Impotence/amenorrhea and/or cardiomyopathy
- High TS and SF

Ferroportin disease

- Caucasian or non-Caucasian, male or female, 10–60 years old
- One parent with unexplained hyperferritinemia
- Unexplained elevation of SF and normal TS





HOW WAS HEMOCHROMATOSIS DISCOVERED ?

HOW DOES HEMOCHROMATOSIS AFFECT DAILY LIFE ?

HOW MANY TYPE OF HEMOCHROMATOSIS ARE THERE ?

CAN HEMOCHROMATOSIS CAUSE MENTAL PROBLEM ?