BRIEF TOUCH OF LOW & HIGH FERRITIN LEVEL

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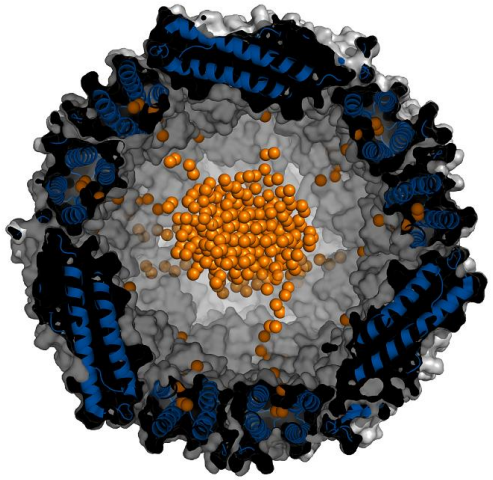
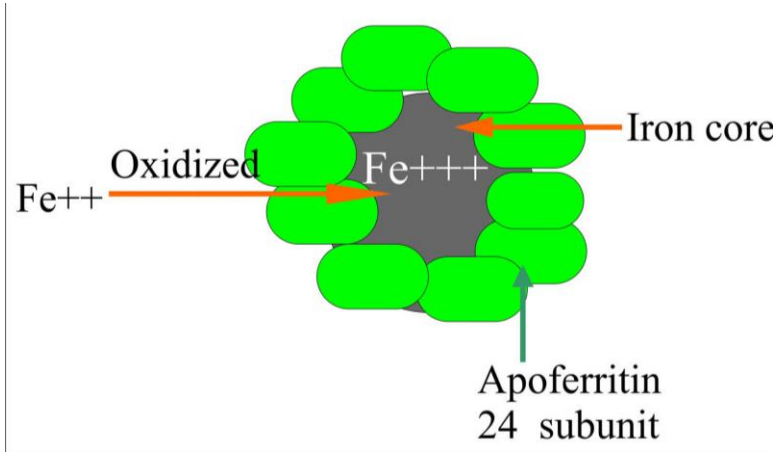
Basics of Ferritin





- A extremely large protein (450 kDa), consisting of a spherical apoprotein shell enclosing a ferric hydroxyphosphate.
- Ferritin is comprised of 24 monomer subunits that consist of either Heavy (H) type (21 kDa) or Light (L) type (19 kDa) polypeptide chains encoded by 2 different ferritin genes.
- Provides intracellular storage of bio-available iron in a safe and readily accessible form.

Biochimica et Biophysica Acta, 1996: 1275, 161–203.

Facts of Ferritin in Humans

- Ferritin is found in all cells and in the highest concentration in liver, spleen and bone marrow.
- Intracellular ferritin is located in the cytosol and in the lysosomes.
- A tiny amount of ferritin is found in the serum. Serum ferritin is almost entirely made up of L chains, has a half-life of 30 h, is not iron-bearing and is some 50–80% glycosylated.
- This serum ferritin (SF) plays no role in iron transport or cellular iron uptake.
- A study of quantitative phlebotomy in normal volunteers showed a correlation between storage iron and serum ferritin concentration with 1 μg/l of serum ferritin equivalent to approximately 8 mg of storage iron.
- Haemosiderin, the “stainable iron” found in iron-laden macrophages, represents insoluble, denatured ferritin from which iron is less readily available.
- Ferritin produced by the lens of the eye consists entirely of L chains. This L chain ferritin is capable of forming crystals under certain conditions, as seen in the hereditary hyper-ferritinemia cataract syndrome (HHCS).

Roles of Ferritin

- In the liver, most ferritin is stored within the parenchymal cells (from plasma transferrin).
- In the spleen and marrow, mainly in macrophages (from break down of RBCs).

- Primary for iron storage, which can store up to 4500 iron atoms as hydrous ferric oxide.

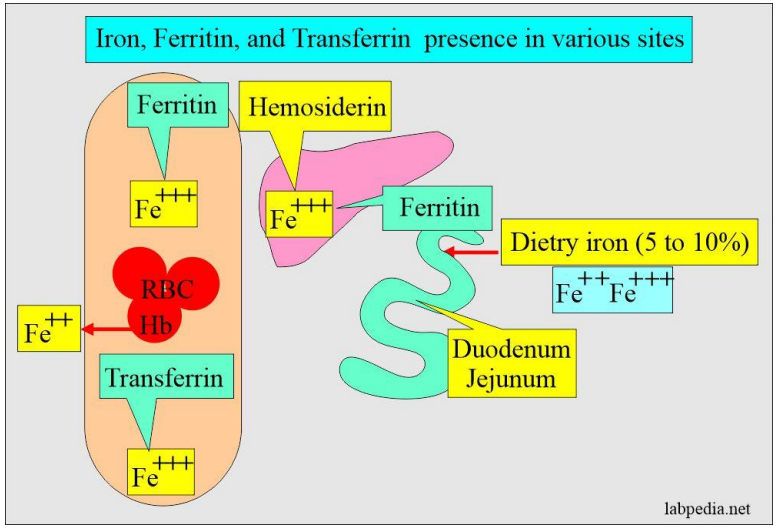
  Ferroxidase activity

  Immune response

  Stress response

  Mitochondria

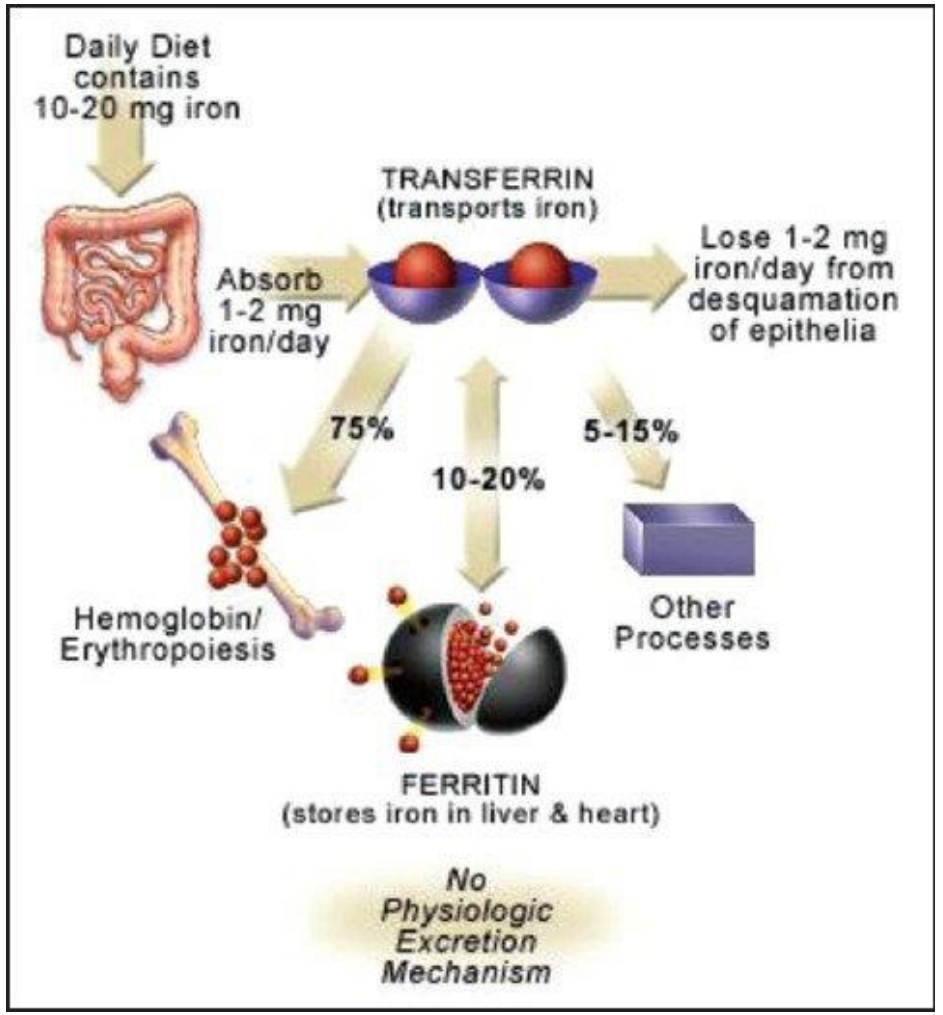
  Form the egg yolk in some species



Blood. 2002, 99: 3505–16.

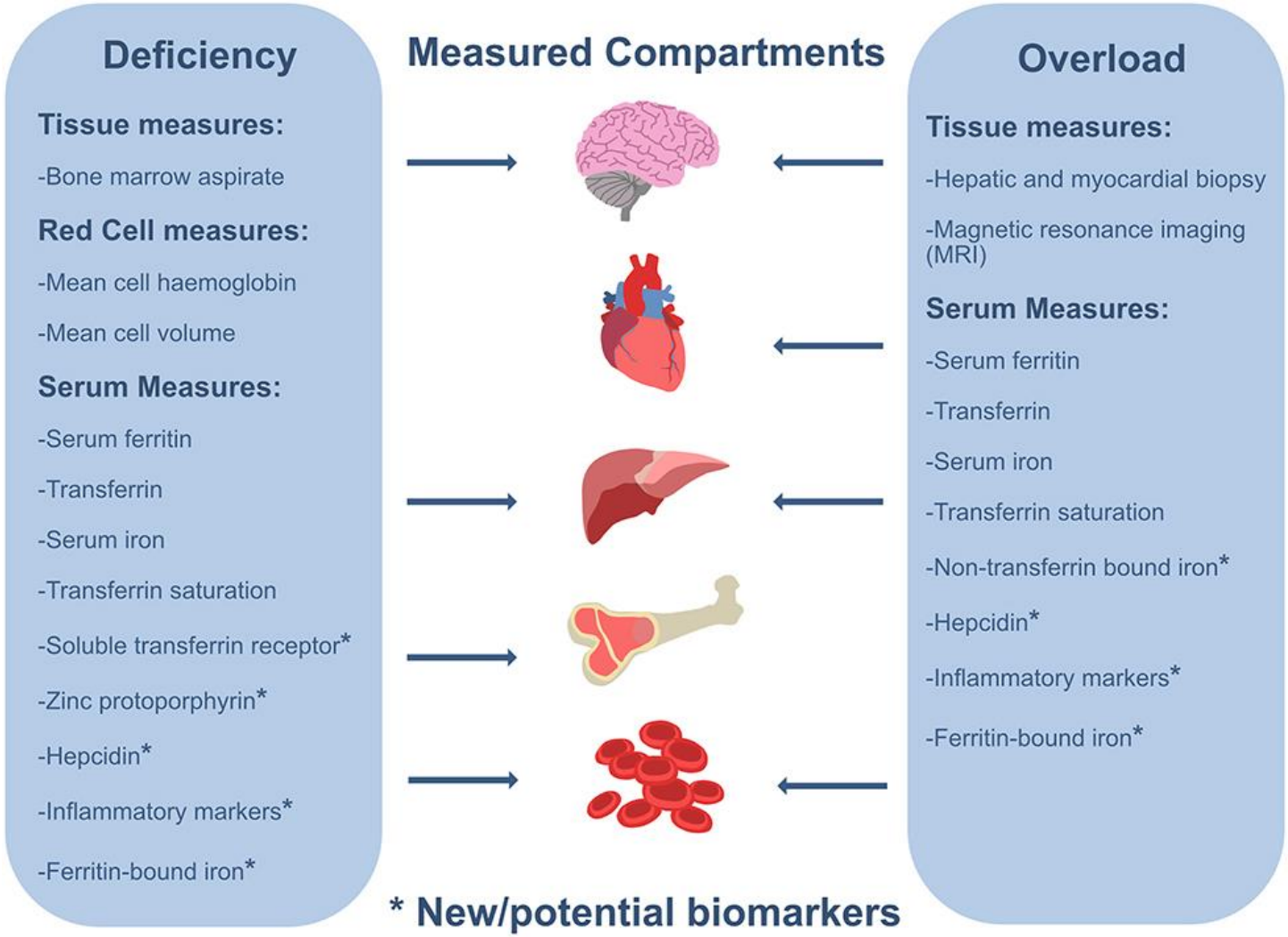
The Journal of Clinical Investigation. 2020:130; 2620–2629.

Ferritin in Iron Metabolism



Ferritin Measurement

Easy Way to Reflect Iron Balance



Clinical Chemistry and Laboratory Medicine (CCLM), 2020.

Variation of Serum Ferritin (SF)

- SF upper limit levels: most labs report 300–400 μg/l in adult males and 150–200 μg/l for adult females.
- Considerable variation: **age**, **ethnic origin** and **gender**.
- Mean SF values in neonates are high (around 200 μg/l) and remain so for about 2 months.
- From 2 to 12 years: approximate 30 μg/l for both boys and girls. Within this age group values >100 μg/l are commonly seen in the context of inflammation, malignancy or juvenile hereditary hemochromatosis.
- At 18 years: SF mean level is higher in males (60–80 μg/l) than in females (25–30 μg/l).
- At 30 years, SF rise to plateau at 120 μg/l in males.
- In adult females, SF only start to rise after 50 years, to plateau of 100 μg/l at 60 years.
- Mean SF values are higher at all ages in adult African males than in adult white males.
- In multi-ethnic population: elevated SF values are found more frequently in Afro-Caribbean and Asian subjects than in whites or Hispanics.
- Very high SF levels > 1000 μg/l are 2–3 times more common in AA and Asian volunteers despite an almost total absence of iron loading genotypes in these 2 populations.

Canadian Journal of Gastroenterology, 2013, 27: 390–392.

Low Ferritin: Clinical Scenarios

-- almost entirely related to reduced iron body storage

- Lack of iron, which could lead to anemia or iron deficiency without anemia.

  The most specific lab finding for IDA but less sensitive. For this reason, low ferritin levels carry more information than those in the normal range.
- Low serum ferritin may indicate hypothyroidism, vitamin C deficiency, or celiac disease.
- Low serum ferritin levels are seen in some patients with restless leg syndrome, not necessarily related to anemia.
- A *falsely low* blood ferritin is very uncommon, but can result from a hook effect of the measuring tools in extreme cases.
- Vegetarianism is not a cause of low serum ferritin levels, though vegetarian adults have lower iron stores than non-vegetarians, their serum ferritin levels are usually within the normal range.

Serum Ferritin (SF) in Dialysis Patients

- SF is not a useful marker of iron stores in patients with chronic kidney disease (CKD), and is elevated in almost half of all patients on maintenance hemodialysis (HD).
- Novel markers for functional iron deficiency, such as percentage hypochromic redcells (%HYPO) or reticulocyte hemoglobin concentration (CHr) have improved clinical utility.
- For CKD patients on treatment with erythropoietic stimulating agents (ESA), iron supplementation should routinely be offered to patients to keep their %HYPO<6% or CHr > 29 pg or Tsat>20% unless heir SF is > 800 μg/l.
- For pts on HD, iron / ferritin markers should be checked every 1–3 months, or every 3 months in pts who are pre-dialysis or on peritoneal dialysis.

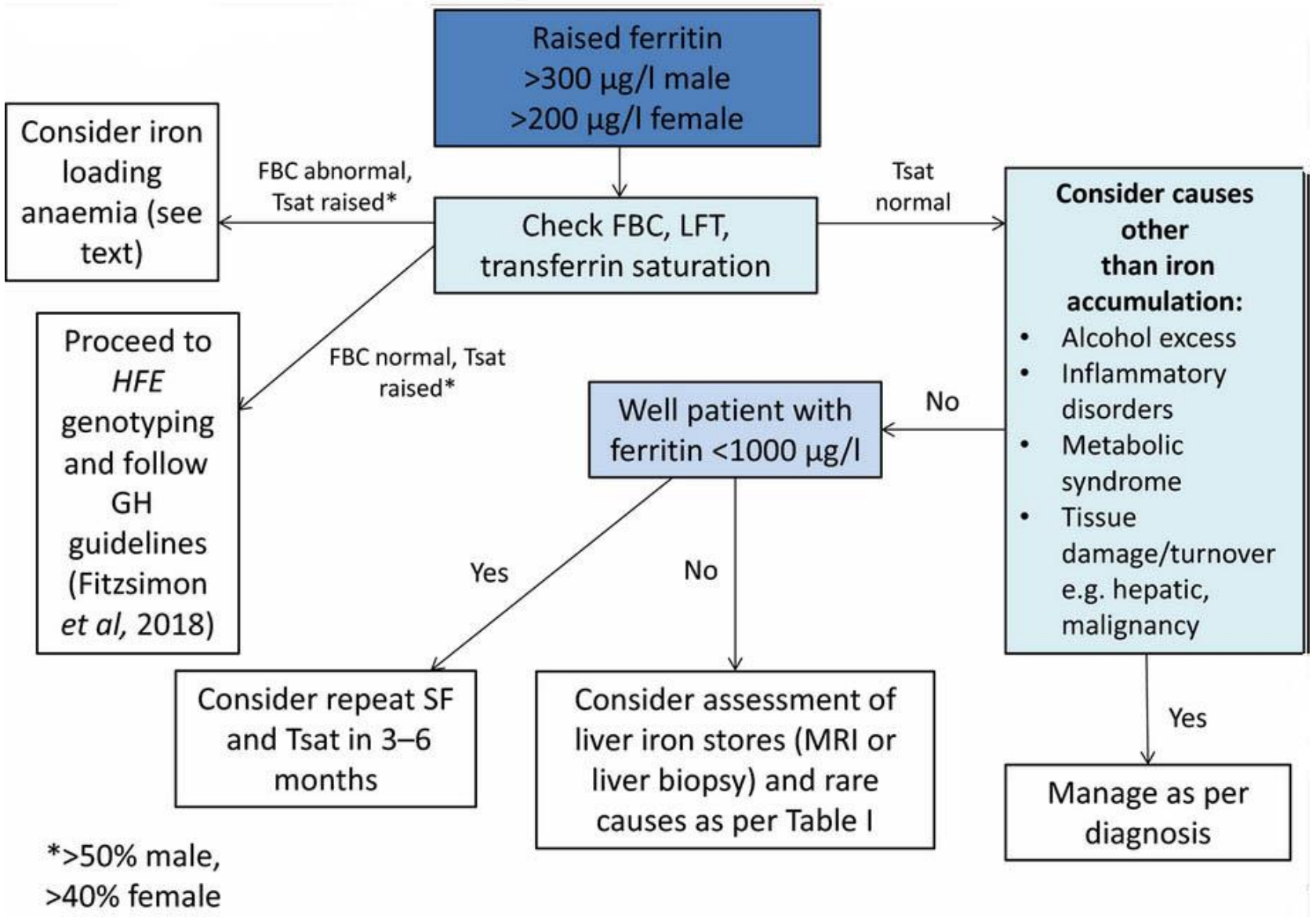
The Renal Association. (2017) Clinical practice guideline – anemia of chronic kidney disease.

Causes of Raised Ferritin

Increased ferritin synthesis due to iron accumulation	**Increased ferritin synthesis not associated with significant iron accumulation**	**Increased ferritin as a result of cellular damage**
Hereditary (genetic) hemochromatosis	Malignancies	Liver diseases: liver necrosis, chronic viral hepatitis, alcoholic and non-alcoholic steatohepatitis
Hereditary aceruloplasminemia	Malignant or reactive histiocytosis	
Secondary iron overload from blood transfusion or excessive iron intake/administration	Hereditary hyperferritinemia with and without cataracts	Chronic excess alcohol consumption
Ineffective erythropoiesis: sideroblastic anemia, some MDS	Gaucher disease	
Thalassemias	Acute and chronic infections	
Atransferrinemia	Chronic inflammatory disorders	
Ferroportin disease	Autoimmune disorders	

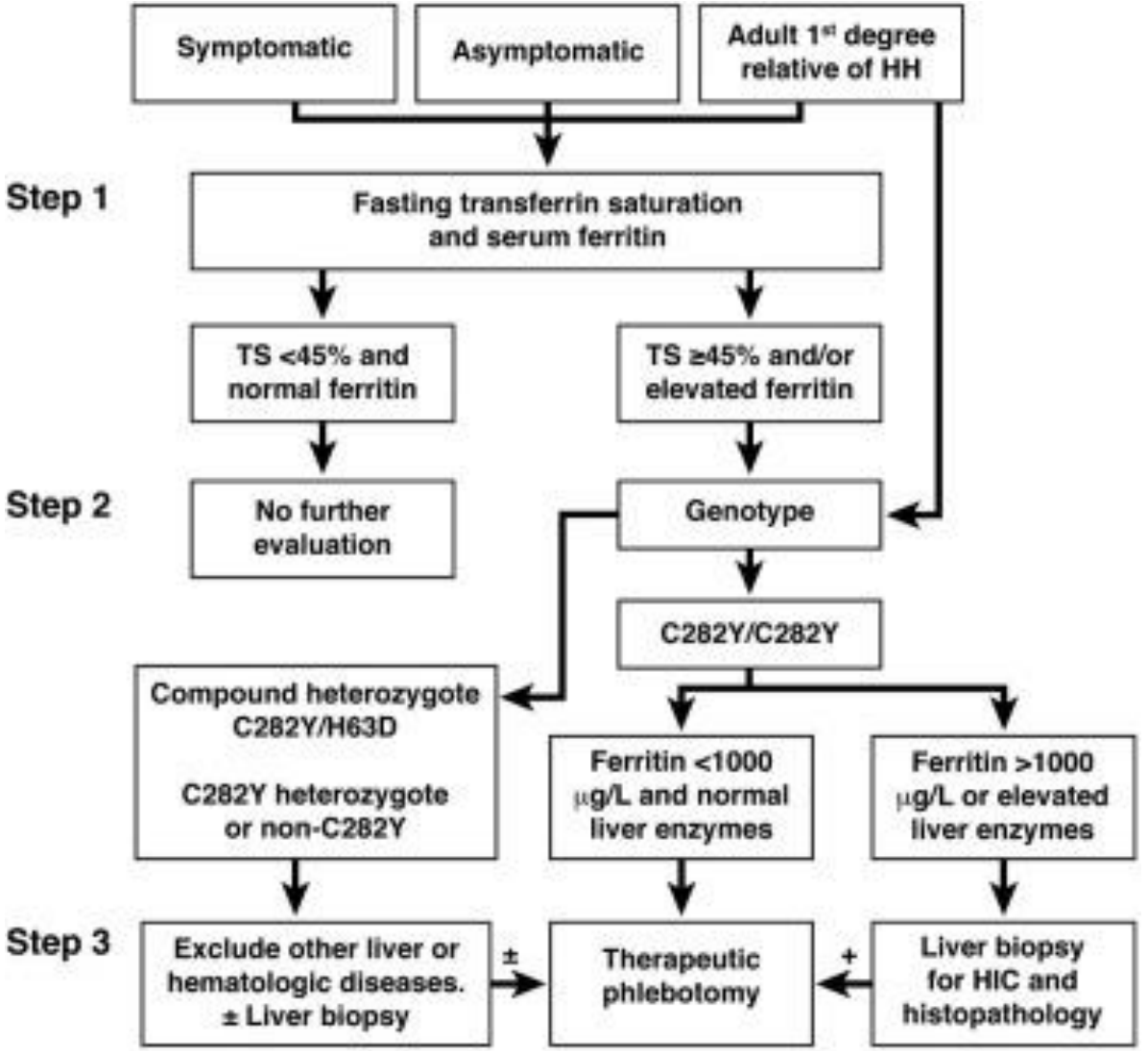
British Journal of Haematology, 2018,181,331–340.

Work Flow for Raised Serum Ferritin Level



British Journal of Haematology, 2018,181,293–303 & 2018,181,331–340.

Work Up For Hemochromatosis



Clinical Gastroenterology and Hepatology. 2012: 10(4): 368.

Ferritin Level in Rare Conditions

- Ferritin and IL-6 are considered to be possible immunological biomarkers for severe and fatal conditionis.
- Markedly elevated serum ferritin levels (>10 000 μg/l) should prompt consideration of rare conditions, such as adult onset Still disease or haemophagocytic lymphohistiocytosis.
- Other rare clinical conditions: SF levels ranging from 400 to 6000 μg/l but did not have raised Tsat levels nor increased liver iron

  Porphyria cutanea tarda

  Hereditary hyperferritinaemia cataract syndrome (HHCS)

  Ferroportin disease

  Atransferrinemia

- Ferritin has been shown to be elevated in some cases of COVID-19 and may correlate with worse clinical outcome. of COVID-19.
- Ferritin and CRP may be possible screening tools for early diagnosis of systemic inflammatory response syndrome in cases of COVID-19.

PLOS ONE. 2021, 16 (6): e0253894.

Summary of Approach for Increased SF

In patients with increased SF, obtaining history:

- alcohol intake
- other risk factors for liver disease
- transfusion history
- family history of iron overload
- the presence or absence of T2DM, obesity and hypertension, as well as for symptoms and signs that may point to an underlying inflammatory or malignant disorder

First line investigations:

- full blood count and film
- repeat serum ferritin
- transferrin saturation
- inflammatory markers (CRP, ESR or plasma viscosity) to detect occult inflammatory disorders
- serum creatinine and electrolytes for renal function
- liver function tests with consideration of viral hepatitis screening and abdominal ultrasonography (if abnormal liver function), and blood glucose and lipid studies

In otherwise well pts with unexplained and moderately elevated SF levels (<800~1000 μg/l) and normal transferrin saturation, a period of observation with lifestyle modification may be reasonable with repeat assessment after 3~6 months.