INVESTIGATION PROTOCOL / GUIDELINE FOR HAEMOCHROMATOSIS

Patient presents To Clinician

TS = fasting transferrin saturation

First degree relative with genetically confirmed HH C282Y/ C282Y Or C282Y/ H63D

Patient with symptoms of hemochromatosis-screen for TS and ferritin

Discovery of persistent raised serum ferritin-screen for TS

Screen for TS and ferritin and proceed to HH Genotyping

TS between 25% -45% consider other causes

TS >45% proceed to HH genotyping

TS > 45%

TS > 45%, consider other causes. Repeat TS in 1-2yrs

Proceed to HH genotyping

REFERENCES
Clinical Penetrance of Hereditary Haemochromatosis. NEJM 2008;358:291-292
Hearnshaw S, Thompson NP, McGill A.
Adams P, Brissot P, Powell LW.
INTERPRETATION OF HFE GENOTYPING RESULTS

C282Y/C282Y (C282Y Homozygote)
Approximately 90% of Irish patients with hereditary haemochromatosis (HH) are homozygous for the C282Y mutation. Gene penetrance is variable and a proportion of individuals with this genotype do not develop clinical haemochromatosis.

C282Y/H63D (Compound Heterozygote)
Approximately, 5% of patients with HH have this genotype. Some patients with this genotype have iron overload but to a lesser degree than C282Y homozygotes.

C282Y/Normal (C282Y Heterozygote)
A small proportion of C282Y heterozygotes exhibit mild to moderately raised indices of iron-overload. Complications due to iron-overload are rare and may be influenced by additional factors, both genetic and environmental.

H63D/H63D (H63D Homozygote)
This genotype is present in about 2% of the population and its role in the development of haemochromatosis remains unclear. The risk of iron-overload in these patients is low.

Procedure for genetic sampling
Discuss with patient and obtain informed consent and complete the HH request form.
Consider referral
C282Y homozygote (C282Y/C282Y) with raised ferritin, compound heterozygotes (C282Y/H63D) with raised ferritin +/- abnormal LFTs.
Patients with liver or endocrine abnormalities should be sent to these sub specialities.

Note: Ferritin <1000 ng/ml is rarely associated with tissue damage. If ferritin persistently >1000 ng/ml,

Pitfalls in diagnosis
Ferritin is a liver synthesised acute phase reactant. Factors causing raised ferritin not related to iron overload include; liver disease, alcohol, chronic inflammation/infection, neoplasia, renal disease, and chronic haemolytic anaemia/ thalassemia.
Medical investigations of secondary causes of elevated ferritin should be led by patients’ symptoms and signs.

It is possible that mutations or polymorphisms in modifier genes are involved in determining a severe disease phenotype in HH. Some rare cases of iron-overload are not linked to mutations in the HFE gene. They are associated with other forms of ‘genetic haemochromatosis’ and linked to mutations in different genes requiring specialist testing.

Some groups may have normal transferrin saturation (TS) but have genetic haemochromatosis. These include: blood donors, women with menorrhagia, children, young women and patients with chronic blood loss/bleeding disorders.

Results, which do not fall into a clear pattern, should be discussed with a Gastroenterologist, Haematologist or Endocrinologist.

Treatment goals
Phlebotomy: All patients with HH and ferritin >4000g/l and rising: venesection once weekly (450-500mls) until serum ferritin is <500g/l and transferrin saturation is <50%.
Maintenance requires regular venesection 2-8 time yearly to maintain TS<50% and Ferritin<50 µg/L