

East Kent Hospitals University NHS

Foundation Trust

**HEREDITARY HAEMOCHROMATOSIS: GUIDELINES FOR BIOCHEMICAL INVESTIGATION AND REQUESTING HFE-GENOTYPING**

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| 1.1 | 02/06/2017 | Mr C Rowe |  | Revised to amend typing error on page 4 |
| 1.2 | 23/06/2017 | Mr C Rowe |  | Page 3. Revised to remove porphyria cutanea tarda as a secondary cause of iron overload |
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**Consultation Schedule**

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| --- | --- |
| **Name & Job Title of Individual / Meeting name**  | **Date consulted**  |
| Dr Sebastian Barton, consultant gastroenterologist | 16th March 2022 |
| Dr Gillian Evans, consultant haematologist | 16th March 2022 |
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**Ratification Schedule**

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| --- | --- |
| **Name of Meeting / Committee**  | **Date approved / authorised**  |
| PMGC | November 2022 |
| CSS Quality and Risk Committee | November 2022 |
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# Introduction, Background and Purpose

This document gives guidance on requesting *HFE* gene analysis in the investigation of hereditary haemochromatosis.

Iron homeostasis is controlled at the level of the gut. The *HFE* gene controls gut iron absorption. Hereditary haemochromatosis (HH) results in uncontrolled iron absorption. Iron overload as a result of haemochromatosis occurs because the body continuously absorbs more iron from the diet than is required. There is no mechanism in the body to excrete excess iron and therefore iron concentrations slowly rise over a number of years, ultimately leading to organ damage. The most common primary cause of iron overload is *HFE-*related HH.

There are also secondary causes that are related to repeated transfusions, iron supplementation and /or increased uptake in GI tract. Secondary haemochromatosis can occur in conditions such as:

* Thalassaemia major anaemia
* Sideroblastic anaemia
* Pyruvate kinase deficiency
* Chronic haemolytic anaemia
* parenteral iron overload
* Hepatitis C and B
* Alcoholic liver disease
* Non-alcoholic fatty liver disease

Hereditary haemochromatosis is caused by mutations in the *HFE* gene. It results in excessive absorption of iron from the diet: the iron is then deposited in various organs, mainly the liver, but also the heart, endocrine glands e.g. pancreas, pituitary, gonads, and joints. Early symptoms may include weakness, lethargy, weight loss and arthralgia. Signs of more advanced disease include skin pigmentation, liver cirrhosis, hypogonadism, diabetes, chondrocalcinosis, cardiomyopathy, hepatocarcinoma and arthritis.

Under physiological conditions a male has a total body iron concentration of approximately 4 g, and a female 3.5 g. Most of the 4 g iron is stored in haemoglobin, contained within red blood cells. Up to 1 g can be stored in the tissues for haem and haemoglobin synthesis. Iron overload occurs when stored iron exceeds 5 g.

In the body, iron is normally stored in the bone marrow; any excess iron in the blood is transported to the liver and the reticuloendothelial system. The liver usually stores a small amount of iron for the essential purpose of providing new red blood cells with iron in the form of haem. Excess liver iron causes liver damage.

The most common form of *HFE* related HH is associated with homozygosity for the A allele in the single nucleotide variant, most commonly known as C282Y. However there is variable penetrance of the clinical phenotype in C282Y homozygotes: 75-85% of individuals do not develop the disease. Genetic screening of the general population screening is not recommended because of the low penetrance of the disease. With *HFE* related haemochromatosis, it is rare for iron to build up to a damaging concentration in childhood, with symptoms and presentation occurring typically in the fourth and fifth decades of life for males and slightly later in females because iron can be excreted during menstruation. Children and adults can however show evidence of iron overload as a result of non *HFE* related or juvenile haemochromatosis, which typically presents before the age of thirty with heart failure and hypopituitarism as common manifestations.

# Definitions

HFE: High Iron (Fe) The HFE gene codes for a transmembrane glycoprotein present as part of the iron uptake channel complex in the small intestine.

Hereditary haemochromatosis (HH): an autosomal recessive disorder caused by a defect in the gene coding for the HFE protein

Iron (Fe): an essential element that is toxic if it accumulates.

Transferrin: an iron binding protein used for transport of iron in the blood.

Ferritin: a protein used to store iron in tissues.

Transaminases: the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

C282Y: the commonest *HFE* mutation causing HH.

# Scope

All staff involved in the requesting of *HFE* genotyping, whether clinical or laboratory must adhere to this guideline.

# Guidance

As with any other laboratory investigation full and explicit clinical details should be provided. All requests will be reviewed before analysis and inappropriate requests will not be processed. A first presentation of *HFE-*related hereditary haemochromatosis is unusual in patients under 40 years old. Consider genetic analysis for non-*HFE* related disorders if there are clinical signs and symptoms and biochemical signs of iron overload. Examples of non-*HFE* disorders:

* Hemojuvelin (HJV)
* Transferrin Receptor-2 (TfR2)
* Ferroportin (SLC40A1)
* Hepcidin (HAMP)
* African iron overload

 **4.1 Initial investigation**

In a patient with suggestive symptoms, physical findings or family history, initial investigations should include **fasting** serum transferrin saturation, ferritin concentration, FBC and LFTs. If ferritin is within the reference range and the transferrin saturation index (TSAT) is ≤40% in females and ≤50% in males then HH is effectively excluded.

 **4.2 Limitations of transferrin saturation index**

The interpretation of iron and transferrin concentrations or TSAT measurements may be compromised by the presence of liver failure, acute phase response, dietary intake (including alcohol) and recent uptake of iron supplements, recent blood transfusion and the presence of haematological diseases (e.g. thalassaemia major). Transferrin is synthesised in the liver and is a negative acute phase reactant; a raised transferrin saturation index can therefore be due to an acute phase response or liver disease. Ideally samples for investigation of iron overload should be taken in the absence of, or after recovery from, infection/inflammation.

**4.3 Ferritin measurement**

Ferritin is a positive acute phase reactant; concentrations increase with infection, inflammation and nonhepatic chronic inflammatory disease. Liver ferritin stores will be released into the circulation in necroinflammatory liver disease (e.g. alcoholic and non-alcoholic liver disease, hepatitis B and C). Measurement of ferritin in the investigation of HH is limited by nonspecific elevations in concentration and also concentrations can be within the reference range in early stages of the disease. An isolated elevated serum ferritin result is commonly seen in dysmetabolic iron overload syndrome as found in the setting of alcohol excess, non-alcoholic fatty liver disease (NAFLD) and other chronic liver diseases and does not reflect haemochromatosis. A raised ferritin concentration in the absence of inflammatory processes and exclusion of other conditions such as alcohol-related liver disease should prompt measurement of transferrin saturation index.

 **4.4 HFE gene analysis**

Requests for *HFE* genotyping will only be processed if at least one of the following criteria is met:

* Transferrin saturation index >40% in females or >50% in males on a **fasting** sample (a non-fasting sample result is acceptable where it is difficult to obtain a fasting sample e.g. critically ill patients) **after** exclusion of other conditions such as alcohol-related liver disease
* Diagnosis of homozygous C282Y *HFE* related haemochromatosis in a first degree relative (siblings, parents and children over the age of consent)
* Exceptional cases (agreed in advance) on an individual patient basis by clinicians and the laboratory. For example, unexplained ferritin concentration persistently greater than 1000 ug/L.

Note, *HFE* testing of minors (<16 y) is not recommended

Requests will **NOT** be processed if one of the following criteria is the only indication:

* Raised ferritin
* Clinically asymptomatic adults with heterozygous C282Y, heterozygous H63D or homozygous H63D *HFE-*related HH in a first degree relative.
* Clinically asymptomatic adults with C282Y/H63D compound heterozygote *HFE-*related HH in a first degree relative.
* Raised transaminases
* Type 2 diabetes
* Arthralgia

*HFE* genetic testing will only be processed on one occasion unless there is doubt over the results. These cases should be discussed with the duty biochemist.

Further investigation of negatives with proven iron overload should be discussed with the duty biochemist. Testing for rarer inherited causes of iron overload (e.g. TfR2 mutations) must be discussed with the duty biochemist.

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# Consultation and Approval

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this guideline.

This document was originally prepared in consultation with Dr Chris Pocock, consultant haematologist and Dr Frank Muller, consultant gastroenterologist.

Consultation has been through e-mail communication between clinical biochemistry staff and medical consultants. CCG leads were also circulated with a draft of this guideline and given the opportunity to comment. Email correspondence is stored on the shared drive.

Revisions made in version 2 were prepared in consultation with Dr Sebastian Barton (consultant gastroenterologist) and Dr Gillian Evans (consultant haematologist)

# Review and Revision Arrangements

Two years from implementation date, by author.

# Training

TrustNet, by proactive implementation through the Care Groups by appropriate clinical leads and by proactive dissemination to primary care partners.

# Document Control including Archiving Arrangements

Archive of this document will be via Q-Pulse, and is responsibility of the owner defined on Q-pulse. The guideline will be hosted on TrustNet and within the Microguide App.

# Monitoring

Within the Trust, compliance with this guideline must rest with the requesting care groups with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional audit within Clinical Biochemistry.

# References and Associated Documents

1. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Bacon BR1, Adams PC, Kowdley KV, Powell LW, Tavill AS; American Association for the Study of Liver Diseases. Hepatology. 2011 Jul;54(1):328-43. doi: 10.1002/hep.24330.
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5. Guidelines on the management of abnormal liver blood tests. Newsome, P.N., Cramb, R., Davison, S.M., Dillon, J.F., Foulerton, M., Godfrey, E.M., Hall, R., Harrower, U., Hudson, M., Langford, A. and Mackie, A., 2017. *Gut*, pp.gutjnl-2017.
6. The effect of alcohol consumption on the prevalence of iron overload, iron deficiency, and iron deficiency anemia.Ioannou, G.N., Dominitz, J.A., Weiss, N.S., Heagerty, P.J. and Kowdley, K.V., 2004. *Gastroenterology*, *126*(5), pp.1293-1301.