Hereditary haemochromatosis: guidelines for biochemical investigation and requesting HFE-genotyping

Version:	1.4
Ratified by:	Clinical Biochemistry Senior Staff Meeting
Date ratified:	29/03/2017
Name of originator/author:	Mr Ceri Rowe/Dr Edmund Lamb
Director responsible for implementation:	Dr Edmund Lamb
Date issued:	03/05/2017
Review date:	3 years from issue date
Target audience:	Healthcare professionals in primary and secondary care

Version control schedule

version	date	author	status	comment
1.0	03/05/2017	Mr C Rowe		
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
1.3	21/12/2017	Mr C Rowe		Page 5. Added alcohol as a cause of raised iron concentrations
1.4	30/08/2018	Mr C Rowe		Page 6. Addition of text under heading 6.1.2

Contents

Section		Page
1	Policy summary	3
2	Introduction	3
3	Purpose and Scope	4
4	Definitions	4
5	Duties	5
6	HFE genotyping: guidelines for requesting	5
7	Key Stakeholders, Consultation, Approval and Ratification process	7
8	Review and Revision arrangements	7
9	Dissemination and Implementation	7
10	Document control including archiving arrangements	7
11	Monitoring Compliance	8
12	References	8

1. Policy summary

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

2. Introduction

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, but there can be secondary causes 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.

3. Purpose and scope

This policy outlines the biochemical abnormalities that support a request for *HFE* genotyping. It is intended for use by healthcare professionals across both primary and secondary care.

4. Definitions

HFE: High Iron Fe.
Hereditary haemochromatosis (HH): an autosomal recessive disorder caused by a defect in the gene coding for the HFE protein present as part of the iron uptake channel complex in the small intestine.
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 and H63D: the commonest *HFE* mutations causing HH.

5. Duties

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

6. Investigating suspected hereditary haemochromatosis

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

6.1 Initial investigation

In a patient with suggestive symptoms, physical findings or family history, initial investigations should include serum **fasting** transferrin saturation and ferritin concentration. If ferritin is within the reference range and the transferrin saturation index (TSAT) is <45% then HH is effectively excluded.

6.1.1 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.

6.1.2 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.

6.2 HFE gene analysis

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

- Transferrin saturation index ≥45% 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) (Note: testing of children is not recommended).
- Exceptional cases agreed on an individual patient basis by clinicians and the laboratory

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

- *HFE* testing of minors (<18 y) is not recommended
- 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.

7. Key Stakeholders, Consultation, Approval and Ratification Process

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

This document has been 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 policy and given the opportunity to comment. Email correspondence is stored on the shared drive.

8. Review and Revision arrangements

Three years from implementation date, by author.

9. Dissemination and Implementation

The guidance will be hosted on the Health Professionals/Pathology area of TrustNet, and will be proactively implemented through the Divisions by appropriate clinical leads and by proactive dissemination to primary care partners.

10. Document control including archiving arrangements

Archive of this document will be via Q-Pulse.

11. Monitoring Compliance

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

12. References

1. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Bacon BR[1], 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.

2. EMQN best practice guidelines for the molecular genetic diagnosis of hereditary hemochromatosis (HH). Porto G[1,2], Brissot P[3], Swinkels DW[4], Zoller H[5], Kamarainen O[6], Patton S[6], Alonso I[1], Morris M[6,7], Keeney S[6,8]. Eur J Hum Genet. 2016 Apr;24(4):479-95. doi: 10.1038/ejhg.2015.128. Epub 2015 Jul 8.

3. Whitfield, J.B., Zhu, G., Heath, A.C., Powell, L.W. and Martin, N.G., 2001. Effects of alcohol consumption on indices of iron stores and of iron stores on alcohol intake markers. *Alcoholism: Clinical and Experimental Research*, *25*(7), pp.1037-1045.

4. Ioannou, G.N., Dominitz, J.A., Weiss, N.S., Heagerty, P.J. and Kowdley, K.V., 2004. The effect of alcohol consumption on the prevalence of iron overload, iron deficiency, and iron deficiency anemia. *Gastroenterology*, *126*(5), pp.1293-1301.

5. 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. Guidelines on the management of abnormal liver blood tests. *Gut*, pp.gutjnl-2017.

Appendix A - Equality Impact Assessment

Equality and Human Rights Impact Analysis (EHRIA)

Part One – Screening Tool

Name of the policy, strategy, function or methodology:	Hereditary haemochromatosis: guidelines for investigation

Details of person completing the EHRIA	
Name	Mr Ceri Rowe
Job Title	Senior Clinical Scientist
Department/Specialty	Pathology/Clinical Biochemistry
Telephone Number	723 6287

1. Identify the policy, strategy, function or methodology aims

What are the main aims, purpose and outcomes of the policy, strategy, function or methodology?
To ensure appropriate investigation of suspected hereditary haemochromatosis across the health service in East Kent.
Does it relate to our role as a service provider and/or an employer?
Service provider.

2. Assess the likely impact on human rights and equality

Use this table to check if the policy, strategy, function or methodology:

- could have a negative impact on human rights or on any of the equality groups, or
- could have a positive impact on human rights, contribute to promoting equality, equal opportunities or improve relations.

It is not necessary to complete each box, nor to mark whether it is positive or negative, although you can do this if you find it helpful.

	Protected Characteristic								
	Race	**Sex**	**Disability**	**Sexual Orientation**	**Religion or belief**	**Age**	**Gender reassignment**	**Marriage & Civil Partnership**	**Pregnancy & Maternity**
Could this policy, procedure, project or service affect this group differently from others? **YES/NO**									
Could this policy, procedure, project or service promote equal opportunities for this group? **YES/NO**									
Right to life *e.g. decisions about life-saving treatment, deaths through negligence in hospital*									
Right not to be tortured or treated in an inhuman or degrading way *e.g. dignity in care, abuse or neglect of older people or people with learning disabilities.*									
Right to respect for private and family life e.g. *respecting lgb relationships, confidentiality*									
Right to freedom of thought, conscience and religion *e.g. respect for cultural and religious requirements*									
Right to freedom of expression *e.g. access to appropriate communication aids*									
Right to freedom of assembly and association *e.g., right to representation, to socialise in care settings*									
Right to education *e.g. access to basic knowledge of hygiene and sanitation*									
Right to liberty e.g. informal detention of patients who do not have capacity									

3. How does it impact on people's human rights and equality?

Using the table above, explain anticipated impacts. If a full EHRIA is recommended, you can summarise the impacts - it is not necessary to set these out in detail,

Could people's human rights be impacted negatively? Could the policy, strategy, function or methodology result in inequality or discrimination?
No
Could this policy, strategy, function or methodology result in positive impacts on people's human rights or equality? Could it present opportunities to promote equality?
No

4. Recommendations

Is a full EHRIA recommended? If not, give reasons
No. The policy has equal impact.

5. Publication of EHRIA

Give details of where Screening Tool or the full EHRIA will be published and when this will take place
With document.

Details of person completing the EHRIA	
Name	Mr Ceri Rowe, Senior Clinical Scientist

Signed …… Date: ……

Approval and sign-off	Name
Head of Department/Director	Mr Edward Kearney, Head of Service Clinical Biochemistry

Signed …… Date: ……

	Name
Trust Board approval and sign-off	not applicable

Signed …… Date: ……

Appendix B – Author's Checklist of compliance with the Policy for the Development and Management of Organisation Wide Policies and Other Procedural Documents

POLICY:

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

	Requirement:	Compliant Yes/No/ Unsure	Comments
1.	**Style and format**	Yes	
2.	**An explanation of any terms used in documents developed**	Yes	
3.	**Consultation process**	Yes	
4.	**Ratification process**	Yes	
5.	**Review arrangements**	Yes	
6.	**Control of documents, including archiving arrangements**	Yes	
7.	**Associated documents**	n/a	
8.	**Supporting references**	Yes	
9.	**Relevant NHSLA criterion specific requirements**	n/a	
10.	**Any other requirements of external bodies**	n/a	
11.	**The process for monitoring compliance with NHSLA and any other external and/or internal requirements**	n/a	

Appendix C – Plan for Dissemination of Policies

To be completed and attached to any policy when submitted to the appropriate committee for consideration and approval.

Acknowledgement: University Hospitals of Leicester NHS Trust (Amended)

Title of document:	Hereditary haemochromatosis: guidelines for investigation		
Version Number:	1.0		
Approval Date:		**Dissemination lead:**	Mr Ceri Rowe
Previous document already being used?	No		
If yes, in what format (paper / electronic) and where (e.g. Directorate / Trust wide)?	n/a		
Proposed instructions regarding previous document:	n/a		

To be disseminated to:	**How will it be disseminated, who will do it and when?**	**Format (i.e. paper or electronic)**	**Comments:**
Trust clinical staff	Trustnet	electronic	
Primary care	Trustnet	electronic	
Clinical Biochemistry staff	Q Pulse	electronic	

Author's Dissemination Record - to be used once document is approved – to be kept with the master document

Date document forwarded to be put on the Trust's central register / in SharePoint:		**Date document put on Directorate register (if appropriate) / on Directorate webpage (if applicable)**	

Disseminated to: (either directly or via meetings, etc.)	**By Whom?**	**Format (i.e. paper or electronic)**	**Date Disseminated:**