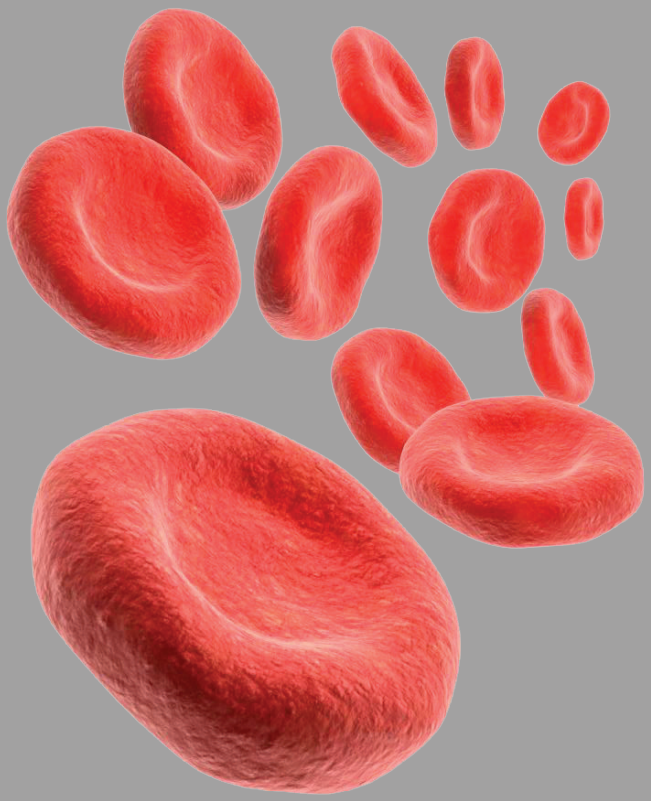
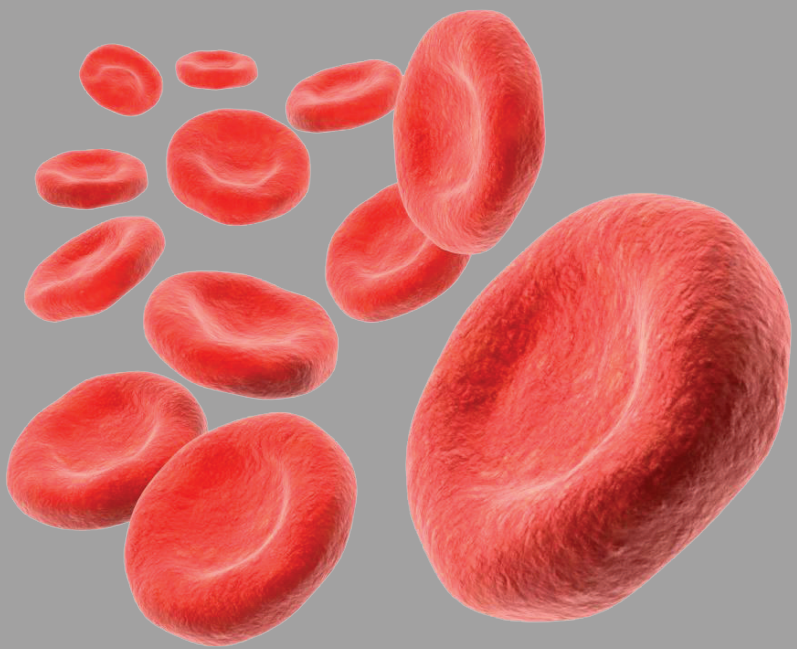


Hereditary Haemochromatosis

Model of Care



Feidhmeannacht na Seirbhíse Sláinte
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Disclaimer

Whilst every effort has been made by the authors and contributors of this document to ensure the information and material contained is complete, accurate and reflects international clinical best practice, errors or omissions may occur.

This guideline aids clinical judgement and does not replace it. In individual cases a healthcare professional may, after careful consideration, decide not to follow the guideline if it is deemed to be in the best interest of the patient.

This guideline should be read in conjunction with *Hereditary Haemochromatosis – Diagnosis and Management from a GP perspective* (1) and Model of Care for Therapeutic Phlebotomy which was produced alongside this document.

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FOREWORD

Ireland has the highest reported prevalence of Hereditary Haemochromatosis (HH) in the world. It is essential that our healthcare system can respond to the needs of patients through the provision of appropriate and timely care. Over the years there have been many attempts to design a more equitable service for patients. In 2015, following a request from the Minister of Health, the HSE undertook to develop a model of care for Hereditary Haemochromatosis and for one of the most important aspects of treatment: Therapeutic Phlebotomy.

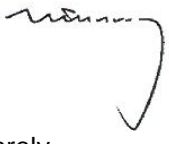
A working group was subsequently established to produce evidence-based guidelines on the diagnosis, screening, treatment and management of patients with HH. After listening to patient concerns, as articulated by the Irish Haemochromatosis Association, it was clear there was significant disparity in the way phlebotomy services are delivered in Ireland. To address this issue and ensure an equitable service for all, recommendations on the delivery and cost of treatment were developed. Our aim was to ensure that the management of patients could be delivered at the lowest level of complexity and in most appropriate setting. For the great majority of patients, this means care in the community, closest to their homes. This is in line with Future Health: A Strategic Framework for Reform which states that patients should be managed through primary care and be referred from primary care only when their needs are sufficiently complex. The MoC reflects these goals.

HH patients constitute a safe source of blood for transfusion and there is a need to align new recommendations with the needs of the Irish Blood Transfusion Service (IBTS). Recommendations have been made to ensure that, where possible, suitable blood is donated to the national blood supply.

These documents would not have been developed without the sponsorship and support of Joe Ryan, Acting Head of the Programme for Health Service Improvement and without the hard work of every member of the Working Group. The project began under the work of Aisling O'Sullivan, Project Manager and then brought to completion by Aisling Phelan, Project Manager. Both Aislings worked tirelessly with members of the working group and the IHA to ensure that we would complete the tasks set by the Minister and meet the expectations of patients. Thanks are also due to Dr. David Hanlon, Dr. Clifford Kiat, Dr. John Lee and Prof. Suzanne Norris who were the principal clinicians involved in the development of the model of care, and to Anna Capplis and Majella Jobling, nurses who run a phlebotomy clinic and who shared much valuable information with us. Thanks also to Noreen Curtin, CIT manager, Dr. Joe Clarke, GP and to Dr. William Murphy for representing the IBTS.

Finally, I would especially like to thank the dedication and hard work of Margaret Mullett, Chair of the Irish Haemochromatosis Association. She has advocated for better care for HH patients for many years with great energy and commitment and has been an articulate and passionate representative of the IHA in their engagements with the HSE and Department of Health.

This model of care outlines an accessible, equitable and quality service. Our collective ambition is now to work to implement these recommendations across all divisions in the HSE.



Sincerely,

Dr. Colm Henry, National Clinical Advisor and Group Lead Acute Hospitals

EVIDENCE BASED MEDICINE

Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.

In this document you will see levels of evidence using the GRADE system (2,3).

	Example	Note	
Quality of evidence			
High	Randomised trials that show consistent results, or observational studies with very large treatment effects.	Further research is very unlikely to change our confidence in the estimate of effect.	A
Moderate	Randomised trials with methodological limitations, or observational studies with large effect.	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	B
Low and very Low	Observational studies without exceptional strengths, or randomized trials with very serious limitations; unsystematic clinical observations (e.g. case reports and case series; expert opinions) as evidence of very-low quality evidence.	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Any estimate of effect is very uncertain.	C
Strength of recommendations*			
Strong	Defined as being 'confident that adherence to the recommendation will do more good than harm or that the net benefits are worth the costs'		1
Weak	Defined as being 'uncertain that adherence to the recommendation will do more good than harm OR that the net benefits are worth the costs'	The uncertainty associated with weak recommendations follows either from poor-quality evidence, or from closely balanced benefits versus downsides	2

* Factors that affect the strength of a recommendation are: (a) quality of evidence; (b) uncertainty about the balance between desirable and undesirable effect; (c) uncertainty or variability in values and preferences; (d) uncertainty about whether the intervention represents a wise use of resources.

ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
EASL	European Association for the Study of the Liver
EFAPH	European Federation of Associations of Patients with Haemochromatosis
EMQN	European Molecular Genetics Quality Network
GP	General Practitioner
HCC	Hepatocellular Carcinoma
HFE-HH	*HFE*-associated hereditary hemochromatosis
HH	Hereditary Haemochromatosis (same as HFE-HH)
HSE	Health Service Executive
IBTS	Irish Blood Transfusion Service
PCT	Porphyria Cutanea Tarda
SF	Serum Ferritin
TS	Transferrin Saturation

GLOSSARY OF TERMS

Care Model	An approved normative healthcare delivery framework
Clinical Governance	Clinical Governance is defined by the HSE as "Corporate Accountability for Clinical Performance" in the domains of quality, safety, access and cost.
Hereditary Haemochromatosis	It is a common inherited disorder in which excessive iron absorption may lead to increased body iron stores with deposition of iron in parenchymal cells of the liver, heart, pancreas and other organs.
HFE-gene	Hereditary haemochromatosis gene with cytogenetic location: 6p21.3
Secondary iron overload	Disorders, other than hereditary haemochromatosis, which give rise to iron overload are classified under the broad heading of secondary iron overload syndromes (usually iron-loading anaemias such as thalassemia major).
Phlebotomy	Incision of a vein for the removal or withdrawal of blood; also called venesection.

EXECUTIVE SUMMARY AND KEY RECOMMENDATIONS

- Hereditary Haemochromatosis (HH) is a common autosomal recessive disease resulting in excessive absorption of dietary iron from the intestine. Over time, excess iron accumulates in the parenchymal cells of organs including the liver, pancreas, heart and anterior pituitary causing damage.
- HH is more common in people of Celtic or northern European decent. It is the most common genetic disease in Ireland with approximately 1 in 83 people predisposed to develop HH (although clinical penetrance is variable).
- Early diagnosis and treatment of the disease prevents organ damage and results in normal life expectancy. Many patients with early stage disease are asymptomatic

Key Recommendations

Signs and Symptoms

I. HH should be suspected in patients with a family history of HH, raised iron studies, liver disease, diabetes, arthritis, skin pigmentation, erectile dysfunction or cardiomyopathy.

Tests Required for Diagnosis and Genetic Testing

II. Patients with suspected iron overload should first receive measurement of fasting transferrin saturation and serum ferritin (Grade 1B) and HFE testing should be performed only in those with increased transferrin saturation (Grade 1A).

III. Laboratories should test for C282Y HFE mutation. According to local practice, H63D can be considered an optional complementary test that can be offered sequentially or simultaneously to C282Y testing.

IV. When a patient meets the referral criteria, requests for HFE genetic testing should be sent to public hospitals to ensure that the patient does not incur the cost of the lab analysis.

Diagnosis

V. The diagnosis of hereditary haemochromatosis is C282Y homozygosity and increased body iron stores with or without clinical symptoms. Diagnosis of HH should not be based on C282Y homozygosity alone, but requires evidence of increased iron stores (Grade 1B).

VI. In C282Y/H63D compound heterozygotes and H63D homozygotes presenting with increased serum ferritin, increased transferrin saturation or increased liver iron additional causes of hyperferritinemia should be considered.

VII. Significant iron overloading occurs principally in C282Y homozygotes. C282Y/H63D compound heterozygosity may be a risk factor predisposing to mild or moderate

forms of iron overload when in association with comorbidity factors, for example, alcohol or metabolic syndrome. The association of homozygosity for H63D with iron overload is debated.

Screening

VIII. Adult siblings (brothers & sisters) of C282Y homozygotes should be screened by testing for HFE gene mutations, and measuring serum iron indices (transferrin saturation and serum ferritin). Genetic testing of other 1st degree relatives should be considered: a) testing adult offspring of C282Y homozygotes is recommended owing to increased risk of C282Y homozygosity and related increased morbidity (Grade 1C). When there are two or more children it may be more cost effective to test the spouse first then offer testing to at-risk adult children only when the spouse carries C282Y b) Parents of C282Y homozygotes should be screened after a clinical decision depending on their age, sex and ferritin.

Treatment

IX. The treatment of haemochromatosis consists of life-long phlebotomy therapy and monitoring of iron indices, in particular serum ferritin. The advocated standard practice is to maintain serum ferritin at 50–100 µg/L. Current practice is that treatment should begin when SF is above the normal range. C282Y/H63D compound heterozygotes and H63D homozygotes may also be appropriate for phlebotomy.

X. Phlebotomy should be carried out by removing 400–500 ml of blood weekly or every two weeks. Adequate hydration before and after treatment, and avoidance of vigorous physical activity for 24 h after phlebotomy is recommended (Grade 1C).

XI. C282Y homozygotes without evidence for iron overload should be monitored yearly and begin treatment when SF rises above normal (Grade 2C). Monitoring of C282Y/H63D compound heterozygotes should also be undertaken.

XII. The goal of dietary management for patients with HH is to eat a balanced, nutritious diet without excessive intake of supplemental iron. Alcohol is a hepatoxin and its consumption should be kept to a minimum.

XIII. Patients should be educated on diagnosis, symptoms and treatment of HH and the importance of life-long management.

1. INTRODUCTION

1.1. BACKGROUND

Hereditary Haemochromatosis (HH) is a common autosomal recessive disease resulting in excessive absorption of dietary iron from the intestine. Over time, excess iron accumulates in the parenchymal cells of organs including the liver, pancreas, heart and anterior pituitary. The accumulated iron eventually leads to the impaired function of these organs, and in its most extreme form, the disease may manifest with potentially life-threatening complications. Early diagnosis and treatment prevent progressive disease, however if left untreated the condition can be fatal with the most common causes of death being decompensated cirrhosis, hepatocellular carcinoma (HCC), diabetes mellitus, and cardiomyopathy (4).

Ireland has the highest levels of this condition in the world (5), with research showing that approximately 1 in 83 people are predisposed to develop hereditary haemochromatosis (5,6).

The treatment for the management of HH is phlebotomy (venesection). Initially the treatment, aimed at reducing the iron in the body tissue to a normal range, may require weekly phlebotomies to reduce ferritin or iron store levels. Once normal levels have been achieved, maintenance may only require 2-4 phlebotomies per year. However, the frequency of maintenance phlebotomy varies among individuals, due to variable rates of iron-re-accumulation (7). In Ireland, the majority of phlebotomies are currently undertaken in acute hospitals.

1.2. OBJECTIVE

The aim of this document was to develop a model of care for HH, outlining recommendations for the standardised approach to the diagnosis, treatment and management of HH, and the conditions for hospital involvement.
This model of care is in line with the 5 Goals of the Health Service Executive Corporate Plan 2015-2017 (8), which are:

1. Promote health and wellbeing as part of everything we do so that people will be healthier;
2. Provide fair, equitable and timely access to quality, safe health services that people need;
3. Foster a culture that is honest, compassionate, transparent and accountable;

4. Engage, develop and value our workforce to deliver the best possible care and services to the people who depend on them;
5. Manage resources in a way that delivers best health outcomes, improves people's experience of using the service and demonstrates value for money.

This document relates to the diagnosis and management of HFE-related haemochromatosis only. The treatment and service for patients with elevated serum ferritin that is due to secondary iron overload conditions, alcohol consumption, metabolic syndrome, obesity, chronic liver disease malignancy, infection or inflammation are not covered in this document.

1.3. WHY THE MODEL OF CARE IS NEEDED

Recommendations to develop an equitable service for patients with HH were published in "*Report of Working Group set up by the Tánaiste in March, 2006 to examine the nature and extent of Haemochromatosis in Ireland and to advise her on the action necessary to address the problems caused by Haemochromatosis*" (9). Efforts to develop a model of care to address these issues have been ongoing with little progress. In 2015, following a request from the Minister of Health, this project was transferred under the joint governance of the HSE Acute Hospital Division (AHD) and the HSE Primary Care Division (PCD). In the absence of a programme of individual clinical lead, the National Clinical Advisor and Group Lead for Acute Hospitals was asked to assume the role for designated lead.

This document is driven by the principles that:

- there is a manifest need for an equitable service for patients with Hereditary Haemochromatosis;
- it can be provided appropriately in primary care in a substantial proportion of cases;
- there is a requirement for structured clinical governance;
- it is in line with established policy of transferring services from acute hospitals to the community where appropriate;
- the needs and wishes of patients will be considered and accommodated to the maximum extent possible, and the interest of patients is paramount;
- the health system, through the Irish Blood Transfusion Service (IBTS) has a legitimate need and social responsibility to maximise the supply and safety of blood donation, a central tenet of which is that donations are made freely and altruistically;
- access to service will be on the basis of clinical need;
- service will be funded on the basis of money following the patient.

Different parts of the country have different clinical pathways for the treatment of HH and there is a need to have a pathway of a care that is patient-centred. This model of care was

developed in tandem with an integrated Model of Care for Therapeutic Phlebotomy which addresses the following principles; phlebotomy carried out at the lowest level of complexity, in the most appropriate setting, and nearest to people's homes.

1.4. DEFINITION

The European Association of the Study of the Liver (EASL) defines Hereditary Haemochromatosis as an *"inherited disorder resulting from an inborn error of iron metabolism, which leads to progressive iron overloading of parenchymal cells in the liver, pancreas and heart. In its fully developed stage, organ structure and function are impaired"* (2).

1.5. CLASSIFICATION

HH is an inherited cause of iron overload, while secondary iron overload syndromes are classified disorders which give rise to iron overload, other than hereditary haemochromatosis. The 2015 European Molecular Genetics Quality Network (EMQN) best practice guidelines (10) details the most recent consensus of classification of Hereditary Haemochromatosis. It was agreed that HFE-related HH is defined by the 2010 EASL Clinical Practice Guidelines for HFE Hemochromatosis *'increased body iron stores associated with homozygosity for the C282Y HFE variant, with or without clinical symptoms'* (2).

The other rare forms of HH are classified as non-HFE-related HH as based on the AASLD Practice Guideline (11). They can be generally defined as *increased body iron stores not associated with homozygosity for the C282Y HFE variant but attributed to pathogenic variants in other iron-related genes,* namely hemojuvelin (HJV), hepcidin (HAMP) and transferrin receptor 2 (TFR2). For all of these genes, the pathogenesis of HH involves inadequate or ineffective production or hepcidin-mediated downregulation of ferroportin with consequent increase in iron absorption and iron export from macrophages. Hepcidin deficiency causes increased transferrin saturation, which is the underlying feature and principal biochemical finding of all forms of HH (10).
There are other genetic causes of severe iron overload, but these should be distinguished from HH because of their distinct clinical and pathological presentation. These include iron-loading anaemias due to ineffective erythropoiesis or due to haemolysis, defects in iron acquisition by the erythroid precursors or repeated blood transfusions (10). All these disorders demand a distinct clinical and molecular diagnosis workup that is out of the scope of the present document.
Table 1 gives a detailed classification of Iron Overload Syndromes.

Table 1. ***Classification of Iron Overload Syndromes*** (10–12)

Hereditary Haemochromatosis (inherited causes of iron overload)	
HFE-related	
	C282Y / C282Y
	C282Y / H63D
	Other HFE mutations
Non- HFE-related	
	Hemojuvelin (HJV)
	Transferrin receptor-2 (TfR2)
	Non-classical Ferroportin disease (SLC40A1)
	Hepcidin (HAMP)
Ferroportin disease	Classical ferroportin disease (SLA40A1)
Secondary Iron Overload	
Iron-loading anaemias	
	Thalassemia major
	Sideroblastic
	Chronic haemolytic anaemia
	Aplastic anaemia
	Pyruvate kinase deficiency
	Pyridoxine-responsive anaemia
Parenteral iron overload	
	Red blood cell transfusions
	Iron–dextran injections
	Long-term haemodialysis
Chronic liver disease	
	Porphyria cutanea tarda
	Hepatitis C
	Hepatitis B
	Alcoholic liver disease
	Non-alcoholic fatty liver disease
	Following portocaval shunt
	Dysmetabolic iron overload syndrome
Miscellaneous	
	Neonatal iron overload
	Aceruloplasminemia
	Congenital atransferrinemia

1.6. PREVALENCE

Hereditary Haemochromatosis is the most common inherited autosomal recessive disorder in the white population particularly those of North European and Celtic descent (13). In Ireland its prevalence exceeds that of cystic fibrosis, phenylketonuria and muscular dystrophy combined (13).

The majority of patients are homozygous for the C282Y mutation in the HFE. The frequency of the C282Y allele is highly variable across Europe. It is 6–8.5% in the United Kingdom and 0% in Southern Europe while the frequency of the C282Y allele in Ireland is 10–12.8%, the highest in Europe (2). The prevalence of the C282Y homozygous state in the Irish population has been estimated at 1:83 (6)(5), see Table 2. This equates to 1.2% of the population or approximately 55,000 individuals (14) with genetic predisposition to HH but not all patients develop symptoms due to variable clinical penetrance (15).

93% of Irish HH patients are C282Y homozygotes, with compound heterozygotes accounting for another 5% (5). C282Y homozygotes are at a higher risk of developing iron overload than C282Y/H63D compound heterozygotes. Even if H63D homozygotes develop elevated serum iron indices, they are less likely to develop total body iron overload.

Table 2. ***Genetic Prevalence in Ireland***

Hereditary Haemochromatosis Prevalence in Ireland (5)	
C282Y Homozygote frequency	1:83
C282Y Heterozygote frequency	1:5
Compound heterozygote frequency	1:60

2. CLINICAL FEATURES

Due to its late and multiple non-specific clinical presentations HH is typically underdiagnosed unless there is increased awareness of the condition. This is of concern as treatment does not completely reverse end-organ damage. Clinical symptoms of HH do not usually appear until between 30 and 40 years of age (2,16). The proportion of C282Y homozygous women with disease manifestation is lower than men of the same age. This later presentation is due to iron loss related to menstruation and pregnancy.

It is important for clinicians to be aware of the symptoms that patients may exhibit to minimise the disparity between the number of patients diagnosed, and the incidence of the condition in Ireland. The AASLD Guidelines (11) states that:

'When patients present with symptoms, hemochromatosis should be considered when there are complaints of fatigue, right upper quadrant abdominal pain, arthralgias, (typically of the second and third metacarpophalangeal joints), chondrocalcinosis, erectile dysfunction, decreased libido, and symptoms of heart failure or diabetes (Table 3). Similarly, physical findings of an enlarged liver, particularly in the presence of cirrhosis, extrahepatic manifestations of chronic liver disease, testicular atrophy, congestive heart failure, skin pigmentation, changes of porphyria cutanea tarda (PCT), or arthritis should raise the suspicion of hemochromatosis (Table 4).' These are not necessary to make a diagnosis. See Table 3 and 4 for symptoms and physical findings in patients with HH.

Table 3. Symptoms in Patients with HH

Asymptomatic
Increased ferritin and transferrin saturation
Abnormal liver function tests (LFTs)
Identified by family screening
Nonspecific, systemic symptoms
Weakness
Fatigue
Lethargy
Apathy
Weight loss
Specific, organ-related symptoms
Abdominal pain (hepatomegaly)
Arthralgias (arthritis)
Diabetes (pancreas)
Amenorrhea (cirrhosis)

Loss of libido, erectile dysfunction (pituitary, cirrhosis)
Congestive heart failure (heart)
Arrhythmias (heart)

Table 4. ***Physical Findings in Patients with HH***

Asymptomatic
No physical findings
Hepatomegaly
Symptomatic
Liver
Hepatomegaly
Cutaneous stigmata of chronic liver disease
Splenomegaly
Liver failure: ascites, encephalopathy, and associated features
Joints
Arthritis
Joint swelling
Chondrocalcinosis
Heart
Dilated cardiomyopathy
Congestive heart failure
Skin
Increased pigmentation (bronzing)
Porphyria cutanea tarda
Endocrine
Testicular atrophy
Hypogonadism
Hypothyroidism

3. DIAGNOSIS

3.1. PENETRANCE AND UNDERDIAGNOSIS

There is considerable variation and controversy surrounding the penetrance of HFE mutations. Some estimates indicate that 15-25% of C282Y homozygous individuals do not develop the disease (17) while another indicates that this figure is as high as 50% (18).

The relationship between HH genotype and phenotype in the Irish population has not yet been examined, but the C282Y homozygote frequency of 1 in 83 is not reflected in the clinical setting (19).
It is unknown how many patients in Ireland have symptomatic HH. Hospital data from 2014 (sourced from Hospital in Patient Enquiry Scheme (HIPE)) showed that there were 20,503 discharges of patients with a diagnosis of haemochromatosis who had a therapeutic phlebotomy (Appendix 2). However, phlebotomy for haemochromatosis performed in out-patient or clinic type settings are not included in this data such as that from St. James Hospital, Dublin and St. Luke's Hospital, Kilkenny. There are estimates that there are 20,000 undiagnosed patients in Ireland with HH. This under-diagnosis may result from lack of awareness of the disease, its long latency period, and its non-specific symptoms, or simply incomplete penetrance (20,21). Many patients are diagnosed on a case-finding basis, some are identified in random health screens, on the basis of family histories or fortuitously.

Due to the high proportion of patients with undiagnosed HH, clinicians should suspect HH in:

- patients with liver disease of unknown cause, including patients with suspected alcoholic liver disease;
- family members of haemochromatosis patients. Note: family members are frequently asymptomatic;
- chronic unexplained fatigue, weakness and abdominal pain;
- asymptomatic patients with incidental elevated LFT, ferritin or hepatomegaly'
- early onset arthralgia (joint pain), atypical arthropathy;
- early onset male impotency, early menopause and loss of libido in women;
- early onset arrhythmias and cardiomyopathy;
- unexplained increasing skin pigmentation or 'permanent tan';
- type 2 diabetes mellitus, especially those diagnosed at an early age, with elevated LFT, hepatomegaly, early-onset sexual dysfunction or abnormal iron markers.

3.2. DIAGNOSTIC CRITERIA

The diagnosis of hereditary haemochromatosis is:
'C282Y homozygosity and increased body iron stores with or without clinical symptoms' (2).

For practical clinical purposes, C282Y/H63D compound heterozygotes and H63D homozygotes are not classified as HFE-associated HH (following the most recent EASL guidelines), and it is recommended that in patients with these genotypes and iron overload, other genetic or environmental risk factors should be examined (10). **These patients may be at-risk of developing mild to moderate iron overload in association with comorbid factors and may be appropriate for therapeutic phlebotomy.**

HH is diagnosed in terms of phenotype (iron overload) and genotype, and is not established by identification of mutated genes alone. The tests used for the diagnosis of hereditary hemochromatosis include transferrin saturation, serum ferritin and genetic testing.

3.3. IRON STUDIES

Patients with hereditary haemochromatosis typically have higher than normal transferrin saturation and serum ferritin as a result of disrupted iron homeostasis (11,12).
The EASL Guidelines state that patients with suspected iron overload should first receive measurement of **fasting serum ferritin and then transferrin saturation (Grade 1B) (2) and HFE testing should be performed only in those with increased transferrin saturation (1A).**

Serum ferritin

Serum ferritin (SF) reflects body iron stores but as an acute phase reactant, can be elevated non-specifically on occasions. It is affected by dietary intake and shows diurnal variation. While low SF is a sensitive and specific indicator of low total body iron stores, elevated SF is considered a highly sensitive but non-specific test for iron overload in hemochromatosis (22,23). Therefore normal serum concentrations can rule out iron overload. It has a low specificity as raised levels can also result from viral infections, inflammatory conditions, metabolic syndrome, cancer, chronic liver disease, drug toxicity and patients on dialysis (2,11,12).

International guidelines recommend the upper limit of normal for serum ferritin of:

- 200 µg/L in pre-menopausal women;
- 300 µg/L in men and post-menopausal women (2,11,12).

Nevertheless, it is recommended to use local reference values as inter-laboratory coefficient of variance of SF concentrations is high at 6-13% (source: Foundation of quality control of medical laboratory diagnostics (SKML) data on interlaboratory variance of serum ferritin from about 270 Dutch laboratories in 2009) (12).

Elevations of serum ferritin in the range of 300 – 1000 µg/L are common, but may be indicative of secondary iron overload. If serum ferritin is ≥1000 µg/L specialist review is required due to the increased risk of fibrosis and cirrhosis above this threshold (23).

In patients with a confirmed diagnosis of HH serum ferritin may be useful in determining cirrhosis and advanced fibrosis (23). Studies have demonstrated that a serum ferritin level of:

- <1000 µg/L is an accurate predictor for the absence of cirrhosis, independent of the duration of the disease (24–26);
- ≥1000 µg/L with an elevated aminotransferase level raises the risk of developing cirrhosis and should be investigated by fibroscan or liver biopsy.

Transferrin saturation

Transferrin saturation (TS) is the proportion of the iron transport protein transferrin that is saturated with iron. It is calculated from the ratio of serum iron (µmol/L) to total iron-binding capacity (g/L) (11,12) and reflects altered iron metabolism. An increased TS reflects increased absorption of iron, the underlying biological defect of this condition. It is more sensitive in detecting early iron overload and is likely to be elevated before serum ferritin increases. In haemochromatosis, transferrin saturation is generally increased during the day, and a non-fasting measurement will detect high values. Raised levels can also be caused by iron loading anaemias, use of iron containing iron supplements, patients with hepatitis and overconsumption of alcohol (12).

Fasting transferrin saturation of ≥45% are strongly suggestive of HH (11,27), with increasing specificity when the threshold is increased to ≥55% (23). The cut-off of ≥45% are considered to have a high sensitivity for detecting C282Y homozygotes and will also identify persons with minor secondary iron overload as well as some C282Y/wild-type heterozygotes, and these cases will require further evaluation (11).

HFE testing should be performed only in those with increased transferrin saturation (Grade 1A) (2). Taken together elevated transferrin saturation (≥45%) and ferritin (above upper limit of normal) have a strong positive predictive value, and their absence give an even stronger negative predictive value of HH (Grade 1B) (2).

3.4. GENETIC TESTING

Based on the EMQN guidelines, it is recommended that (10):

- Laboratories providing testing for HFE-associated HH should test for C282Y (Grade 1A).
- According to local practice, H63D can be considered an optional complementary test that can be offered sequentially or simultaneously to C282Y testing (Grade 2C).
- It is recommended that testing laboratories are accredited according to international standards (ISO 15189 or equivalent).
- Testing for S65C should not be offered; if detected as an incidental finding, it should not be reported (Grade 1B).

The association with haemochromatosis with HFE variants other than C282Y is still debated and no established consensus has been published (10). C282Y/H63D compound heterozygotes and H63D homozygotes presenting with increased serum ferritin (>200 µg/L in females, >300 µg/L in males), increased transferrin saturation (>45% in females, >50% in males) or increased liver iron should first be investigated for other causes of hyperferritinemia (Grade 1C) (2). Table 5 documents the interpretation of HFE gene C282Y and H63D related genotypes.

C282Y/H63D compound heterozygosity may be a risk factor predisposing to mild or moderate forms of iron overload when in association with comorbidity factors, for example, alcohol or metabolic syndrome (2,28). The association of homozygosity for H63D with iron overload is debated and requires further clinical research, but it is now recommended that other risk factors or other genetic causes should be sought and investigated in patients with this genotype and demonstrated iron overload (29).

Table 5. Summary of diagnostic and predictive interpretation comments for the HFE gene C282Y and H63D related genotypes. Taken from EMQN Guidelines (10).

Genotype	*Interpretation (diagnostic test)*	*Interpretation (predictive test)*
Homozygous C282Y	Compatible with the diagnosis of HFE-related HH in the presence of documented evidence of iron overload.	At risk of developing HFE-related HH. Prompt assessment of iron parameters indicated.
Compound heterozygous C282Y/H63D	Excludes the diagnosis of the most common form of HFE-related HH; genotype consistent with mild to moderate iron overload; Prompt the search for other causes (eg, alcohol consumption, fatty liver disease and/or metabolic syndrome).	At low risk for development of significant iron overload. May be at-risk of developing mild to moderate iron overload in association with comorbid factors.
Heterozygous C282Y	Excludes the diagnosis of the most common HFE-related HH. Other causes of iron overload should be considered.	Carrier for HFE-related HH. Is at no increased risk of developing HFE-related HH.
Homozygous H63D	Excludes the diagnosis of the most common HFE-related HH. Other causes of iron overload should be considered.	May develop iron-overload in association with other risk factors or other genetic causes.
Heterozygous H63D	Excludes the diagnosis of the most common HFE-related HH. Other causes of iron overload should be considered.	At no increased risk of developing HFE-related HH.
S65C detected	In the absence of supporting evidence for a role in HH, testing for the S65C variant is not recommended for diagnostic purposes. If detected as an incidental finding it should not be reported but treated as 'no variant detected'.	

A systematic review found sensitivity and specificity of C282Y homozygosity to be about 90% and almost 100% respectively, for the presence of an iron overload phenotype in white northern Europeans (30). Note that mutations in 5 different genes are known to cause iron overload thus testing of 'other hemochromatosis genes' (TFR2, SLC40A1, HAMP, HJV) could be considered in patients with increased iron stores after exclusion of C282Y homozygosity if (i) iron excess has been proven by direct assessment, i.e. by MRI or liver biopsy, and (ii) other hepatic and haematological disorders have been ruled out (Grade 2C) (2).

Whereas the HFE gene test indicates the risk of eventually developing iron overload, iron studies indicate if iron overload is currently present. The HFE gene test is performed once,

whereas iron studies are performed every time an assessment of current iron overload is required (23).
Please see Appendix 3 for information on Data Protection and Insurance in Genetic Testing

3.5. REQUEST FOR GENETIC TESTING

There is significant disparity in payment arrangements regarding HH genetic testing. Where patients are seen by a consultant in a hospital, they do not incur lab analysis costs. When a GP sends in a genetic test request to a hospital, the hospital typically pays the cost. However, this practice is not uniform, and in some locations, the cost of testing is passed on to the patient. Some GP's send HFE requests directly to private labs, thus also placing the cost of the analysis on the patient. In addition, patients report that it can take considerable time to get a genetic test result back from a hospital. Some GP's send to private labs for a faster turnaround time.

Overall, there is not equity in the provision of genetic testing nationally and this needs to be addressed.

The working group recommend that:

- HH genetic testing should be centralised to one or a few regional centres. This would allow the development of a database of patients with HH and be more cost effective for the health service.
- When a patient meets the referral criteria, requests for Hereditary Haemochromatosis genetic testing should be sent to public hospitals to ensure that the patient does not incur the cost of the lab analysis.

3.6. LIVER BIOPSY

Liver biopsy historically was the gold standard for the diagnosis of HH before HFE genotyping became available. Liver biopsy allows histological staining of iron and measurement of hepatic iron concentration. Importantly, liver biopsy remains the most reliable way to determine the presence of cirrhosis and advanced fibrosis (2,11). This is relevant as patients with cirrhosis are at risk of hepatocellular carcinoma (HCC) and other life-threatening complications of cirrhosis such as oesophageal variceal haemorrhage. The risk of HCC persists in cirrhotic patients even after adequate treatment of iron overload (31) and ongoing surveillance of HCC should continue.

Liver biopsy should be considered in HH patients with (2,31):

- serum ferritin above 1000 µg/L (Grade 1C);
- history of alcohol abuse;
- elevated AST (Grade 1C);
- hepatomegaly on clinical exam (Grade 1C);
- age over 40 years (Grade 1C).
- hepatitis B/C or Steatohepatitis.

Liver biopsy does not need to be performed when ferritin is <1000 µg/L, in the absence of excess alcohol consumption and elevated serum liver enzymes (2,31).

Patients with elevated serum iron studies, but who lack C282Y homozygosity, should be considered for liver biopsy if they have elevated liver enzymes or other clinical evidence of liver disease. These patients may have non-HH liver disease such as NAFLD, ALD or chronic viral hepatitis (11).

3.7. IMAGING

The Role of Imaging Techniques

When there is sufficient iron overload, the attenuation value of the liver on computed tomography increases. However, the sensitivity is insufficient using standard settings to detect lower levels of iron accumulation, and therefore this technique is not useful for screening or follow-up (32).

Magnetic resonance imaging (MRI)

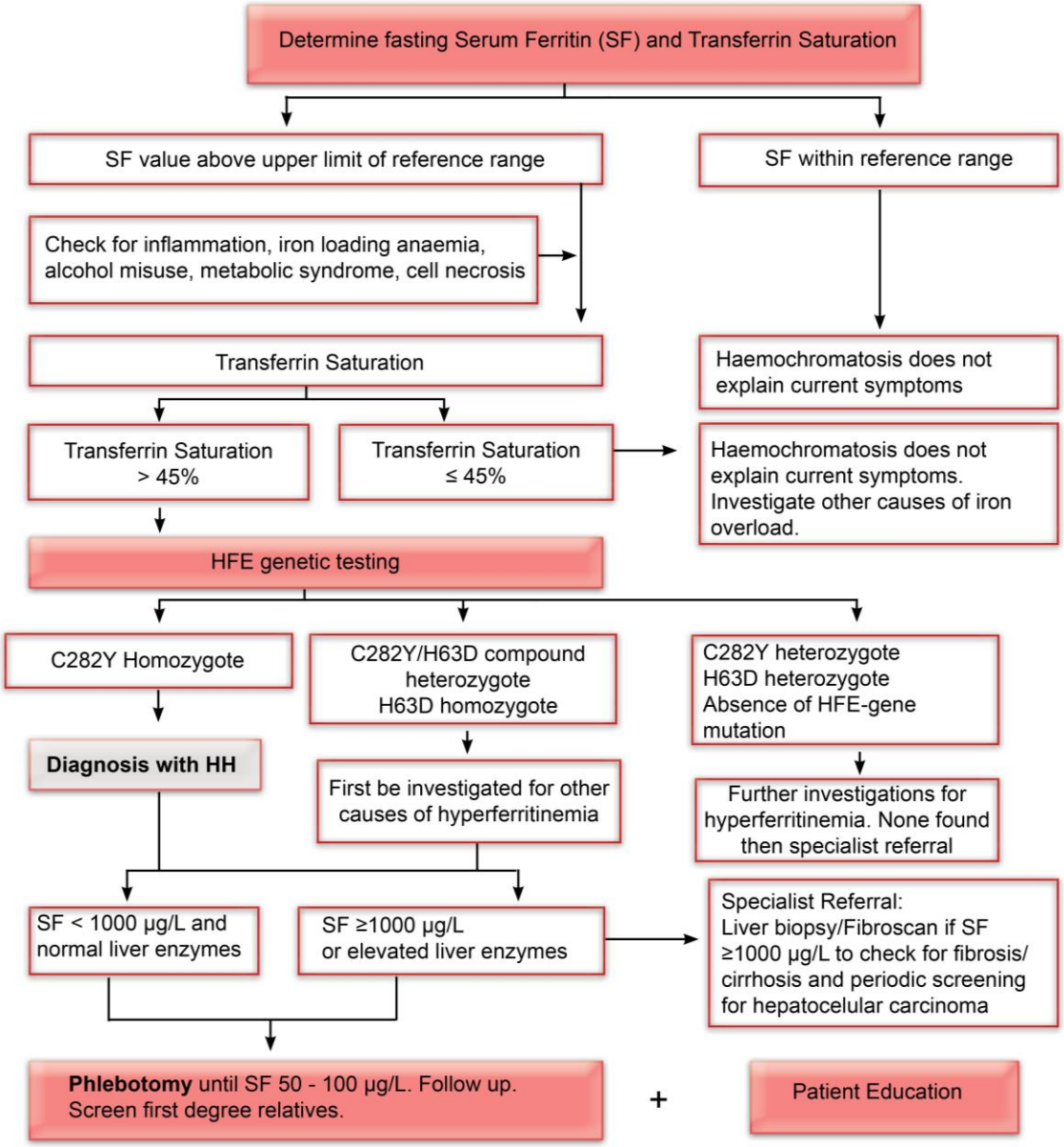
If the diagnosis is still unsure after blood analysis and testing for the C282Y and H63D polymorphisms of the HFE gene, MRI can be considered (12). Magnetic susceptibility is a very powerful technique allowing quantitation of hepatic iron levels from low to very high but is not at present widely available (1). The MRI can detect and quantify iron but expertise is needed to use this approach clinically for evaluation of iron overload or follow-up (32). There is a reliable inverse correlation between MRI signal and biochemical hepatic iron concentration (HIC) allowing for the detection of hepatic iron excess within the range 50–350 μmol/g with a 84–91% sensitivity and a 80–100% specificity according to cut-off levels of HIC ranging from 37 to 60 μmol/g wt. (33,34).

Fibroscan

Transient elastography, a special form of ultrasound, has a role in staging fibrosis as an alternative to liver biopsy (35). It is known by the brandname FibroScan and is a non-invasive test to quantify liver fibrosis by measuring liver stiffness. A study published by Adhoute et al. in 2008 (35) concluded that biochemical markers and FibroScan may constitute reliable non-invasive means for liver fibrosis determination. It is not however a measure of iron quantity in the liver.

3.8. APPROACH TO TESTING

Diagnostic flowchart for patients with suspected Hereditary Haemochromatosis based on (12,26)



3.9. WORK-UP

After diagnosis with HH, management is guided by the SF concentration.

- If SF is normal, follow up once a year is recommended.
- If SF is elevated, initial evaluation should include fasting blood glucose, HbA1c, serum AST, and ALT activity. Further tests should be ordered according to the clinical features (liver biopsy should be considered in patients with SF >1000, ECG, Chest X-ray and X-ray of affected joints, and other biochemical tests may also be considered, depending on the clinical presentation. These may require specialist referral, see Section 6.3.)

The clinician should be looking out for complications relating to general health (physical asthenia), the skin (pigmentation), liver (hepatomegaly, fibrosis, cirrhosis, hepatocellular carcinoma), joints (joint disease, articular chondrocalcinosis, osteoporosis), endocrine functions (diabetes) or the heart (restrictive cardiomyopathy) (36).

The patient should also be given advice about risk factors such as alcohol abuse and viral liver disease (e.g. vaccination against hepatitis B). See Section 6 for details on patient education.

Summary Recommendations for Diagnosis:

- Patients with suspected iron overload should first receive measurement of fasting transferrin saturation and serum ferritin (Grade 1B) and HFE testing should be performed only in those with increased transferrin saturation (>45%) (Grade 1A).
- Laboratories should test for C282Y HFE mutation. According to local practice, H63D can be considered an optional complementary test that can be offered sequentially or simultaneously to C282Y testing.
- The diagnosis of hereditary haemochromatosis is C282Y homozygosity and increased body iron stores with or without clinical symptoms.
- Significant iron overloading occurs principally in C282Y homozygotes. C282Y/H63D compound heterozygosity may be a risk factor predisposing to mild or moderate forms of iron overload when in association with comorbidity factors, for example, alcohol or metabolic syndrome. The association of homozygosity for H63D with iron overload is debated.
- In C282Y/H63D compound heterozygotes and H63D homozygotes presenting with increased serum ferritin (>200 µg/L in females, >300 µg/L in males), increased transferrin saturation (>45% in females, >50% in males) or increased liver iron additional causes of hyperferitenmia should be considered. These patients may be appropriate for therapeutic phlebotomy.
- All patients with evidence of liver disease should be evaluated for haemochromatosis
- Liver biopsy should be undertaken in HH patients with serum ferritin above 1000 µg/L, elevated AST, hepatomegaly, age over 40 years (Grade 1C).
- Liver biopsy does not need to be performed when ferritin is <1000 µg/L, in the absence of excess alcohol consumption and elevated serum liver enzymes.

See Appendix 4 for quick reference table for confirming the diagnosis of Hereditary Haemochromatosis and the management of a patient with different iron study results, adapted from the British Committee for Standards in Haematology 2010 (32).

4. SCREENING

4.1. FAMILY SCREENING

Due to the autosomal recessive transmission of HH, genetic testing should be carried out to detect early disease and prevent complications on the following patients (based on recommendations as per EMQN Guidelines (10)):

- Testing adult siblings (brothers and sisters) of C282Y homozygotes is recommended owing to the increased risk of C282Y homozygosity and related increased morbidity (Grade 1B).
- Testing adult offspring of C282Y homozygotes is recommended owing to increased risk of C282Y homozygosity and related increased morbidity (Grade 1C). When there are two or more children it is more cost effective to test the spouse first (38) then offer testing to at-risk adult children only when the spouse carries C282Y.
- Testing asymptomatic parents of C282Y homozygotes is not recommended systematically but rather as a clinical decision depending on their age, sex and ferritin, all three influencing the probability to develop severe iron overload (Grade 1C).
- Systematic testing of adult first-degree relatives of C282Y heterozygotes is not currently recommended, in the absence of evidence of benefit (Grade 2C).
- HFE testing of minors is not recommended (Grade 1B). Note there have been no reports of iron overload from C282Y homozygosity occurring before the age of 18 years (37).

For ease of testing, both genotype (HFE mutation analysis) and phenotype (SF and TS) should be performed simultaneously at a single visit.

The EMQN Guidelines (10) states that owing to the relatively low risk of morbidity and the consequently low clinical efficiency of screening, consensus was not reached in order to recommend genetic testing of clinically asymptomatic adults of first degree relatives for C282Y/H63D compound heterozygotes. Genetic testing of clinically asymptomatic adult first degree relatives of C282Y heterozygous or H63D homozygotes is not recommended (10). However, the working group agree that in an Irish context, genetic testing or monitoring of iron indices may be considered on a case by case basis of these patient's first degree relatives.

After testing is completed the interpretation of results should follow Table 5. Detailed best practice reporting guidelines can be found in the EMQN Guidelines (10) and should be followed. The AASLD guidelines state that (11):

- If C282Y homozygosity or compound heterozygosity is found in adult relatives and if serum ferritin levels are increased, then therapeutic phlebotomy can be initiated (11).
- If ferritin level is normal in these patients, then yearly follow-up with iron studies is indicated (11).
- When identified, C282Y heterozygotes and H63D heterozygotes can be reassured that they are not at risk for developing progressive or symptomatic iron overload, although they may have minor abnormalities in serum iron measurements such as TS or SF (11).
- Occasionally, H63D homozygotes can develop mild iron overload (11).
- Any of these genotypes can be a cofactor for the development of liver disease when they occur in conjunction with other liver diseases such as PCT, hepatitis C infection, ALD, or NAFLD (11).

A letter could be sent to all first degree relatives of a patient diagnosed with HH after consultation with the patient and obtaining the patients' consent. Please see Appendix 5 for an example family member letter.

4.2. POPULATION SCREENING

Several authors have suggested population screening due to the high prevalence of the C282Y homozygous genotype in European populations. However, international guidelines (2,10,26,31) agree that the low clinical penetrance means that many people would be incorrectly diagnosed with HH. Thus, population screening for C282Y variant is not currently recommended (Grade 1B) (2).

The EASL Guidelines recommend screening in the following patient populations (2):

- HFE testing should be considered in patients with unexplained chronic liver disease pre-selected for increased transferrin saturation (Grade 1C).
- HFE testing could be considered in patients with:
    - Porphyria cutanea tarda (Grade 1B);
    - Well-defined chondrocalcinosis (Grade 2C);
    - Hepatocellular carcinoma (Grade 2C);
    - Type 1 diabetes (Grade 2C).
- HFE testing is **not** recommended in patients with:
    - Unexplained arthritis;
    - Type 2 diabetes (Grade 1B).

4.3. SCREENING FOR NON-HFE RELATED HH

The term ''non–HFE-related HH'' refers to several genetically distinct forms of inherited iron overload affecting individuals without HFE mutations (39). Several of the genes involved are hemojuvelin (HJV), ferroportin (SLC40A1), transferrin receptor 2 (TFR2), and hepcidin (HAMP). The non-HFE forms of inherited iron overload are rare, accounting for <5% of cases encountered, and genetic testing is largely unavailable except in research laboratories. Screening for non–HFE-related HH is not recommended (26) except for certain cases such as evidence of iron overload, confirmed on liver biopsy, and negative HFE gene mutations. It is recommended that genetic testing for suspected rare forms of haemochromatosis should only be considered by specialist centres (10).

5. TREATMENT FOR HEREDITARY HAEMOCHROMATOSIS

5.1. TREATMENT

Three approaches have been used to remove excess iron:

- **Therapeutic Phlebotomy: mainstay of treatment;**
- Iron chelation: Iron chelators are available and can be an option in patients who are intolerant or when phlebotomy is contraindicated;
- Erythrocytophoresis: reported in treatment of HH but is not widely practiced.

***Therapeutic Phlebotomy*[1]**

Treatment for haemochromatosis consists of lifelong phlebotomy and monitoring of iron indices, in particular SF. Phlebotomy therapy depletes the body of iron by removal of iron in haemoglobin. 500ml of blood contains approximately 250mg of iron (2). The concentration of iron above which phlebotomy is indicated is not clear. A consensus based approach is to start treatment when SF rises about local reference values (typically 300 µg/L and 200 µg/L for men and women, respectively) (2).

The optimum frequency of phlebotomy and quantity of blood taken are unclear, but expert consensus suggest that 500mL should be taken each week in the depletion stage, guided by SF and haemoglobin values (2,11). No evidence is available to set a target value for SF. The EASL and AASLD guidelines aim for 50-100 µg/L. However, some reports suggest aiming for values within the normal range because these might be better tolerated by patients, result less often in anaemia, and present an increase in intestinal iron uptake caused by further lowering of hepcidin as a result of intensive bloodletting (29). The maintenance stage is reached when SF drops below the target value. The optimum frequency of phlebotomy will depend on the patients symptoms and response to treatment, the SF value at diagnosis and patient preferences (12).

People with C282Y/H63D and H63D/H63D in general do not have the same susceptibility to parenchymal iron overload and end organ damage as C282Y homozygotes and may not need an aggressive approach to phlebotomy therapy. Careful consideration should be given to the indications for and frequency of phlebotomy therapy in these subjects and ferritin levels should be closely monitored during their treatment course (40).

[1] The Model of Care for Therapeutic Phlebotomy details the locations where phlebotomy will be carried out and the policies and procedures for therapeutic phlebotomy.

Treatment of Hemochromatosis, based on the EASL Guidelines (2) and AASLD Guidelines (11) is as follows:

- Patients with HH and evidence of excess iron (SF exceeds the threshold of 300 µg/L in men and 200 µg/L in women) should be treated with phlebotomy (Grade 1C).
- Patients with HH without evidence for iron overload should be monitored annually and treatment instituted when the ferritin rises above normal (Grade 2C).
- Before the initiation of phlebotomy, patients with HH should be assessed for complications including liver disease, diabetes mellitus, joint disease, endocrine deficiency (hypothyroidism), cardiac disease, porphyria cutanea tarda.
- The initiation of phlebotomy should be carried out by removing 400–500 ml of blood (200–250 mg iron) weekly or every two weeks (Grade 1A). Adequate hydration before and after treatment, and avoidance of vigorous physical activity for 24 h after phlebotomy is recommended (1C). Target levels of phlebotomy should be a SF level of 50 - 100 µg/L (Grade 1B).
- Check haematocrit/haemoglobin and serum ferritin prior to phlebotomy:
    - every 4-6 phlebotomies during treatment phase.
    - every phlebotomy during maintenance phase.
    - or as clinically indicated e.g. comorbidity such as renal impairment

  Allow haematocrit/haemoglobin to fall by no more than 20% of prior level.
- Stop frequent phlebotomy when serum ferritin reaches 50-100 µg/L. As the target range of 50-100 µg/L is approached, testing may be repeated more frequently to pre-empt the development of overt iron deficiency.
- Once iron levels are at target range of ferritin 50-100 µg/L, patients usually require one phlebotomy every 3 to 4 months to keep levels low without rendering the patient iron-deficient. Note, for reasons that remain unclear, not all patients with HH reaccumulate iron and therefore may not need maintenance phlebotomy regime. Target levels of phlebotomy should be a ferritin level of 50 and 100 µg/L (Grade 1B).
- In the absence of indicators suggestive of significant liver disease (ALT, AST elevation) patients who have an elevated ferritin (but <1000µg/L) should proceed to phlebotomy without a liver biopsy (Grade 1B).
- Patients with end-organ damage due to iron overload should undergo regular phlebotomy to achieve SF target range (Grade 1A).
- Complications of HH (liver cirrhosis, diabetes, arthropathy, hypogonadism, PCT) should be managed regardless of whether or not HH is the underlying cause and whether there is symptomatic relief or improvement during phlebotomy (Grade 1C).
- To minimise the risk of additional complications, patients with HH could be immunized against hepatitis A and B while iron overloaded (Grade 2C).

In patients with HH who may have total body iron stores >30g, therapeutic phlebotomy may take up to 2-3 years to adequately reduce iron stores (11).

Contraindications

Permanent and temporary or transient contraindications are given below in Table 6, based on 'Management of patients with HFE-related haemochromatosis (Type 1 haemochromatosis)' (36).

Table 6. Contraindications to phlebotomy

Permanent contraindications

- any disease likely to compromise the patient's health during phlebotomy
- sideroblastic anaemia or any other form of anaemia caused by inadequate haemoglobin production and not by deficiency
- thalassaemia major
- severe or uncontrolled heart disease not secondary to haemochromatosis
- unstable or severe coronary disease, severe cardiomyopathy, left heart valve disease, uncontrolled heart failure, poorly-tolerated ventricular or supraventricular arrhythmias, etc. (a cardiologist should be consulted to establish the severity of the disorder).

Temporary and/or transient contraindications

- major iron deficiency anaemia (< 11 g/dL, particularly when this may be the result of previous phlebotomies)
- hypotension (SBP < 100 mmHg)
- severe occlusive arterial disease of the lower limbs, history of acute thrombotic ischaemia of a limb artery, or recent stroke (< 6 months)
- heart rate < 50 or > 100 bpm
- pregnancy (there is no major risk in suspending treatment for 9 months; during the 6 months following delivery, the reference serum haemoglobin threshold for blood donations is proposed to be 12.5 g/dL
- if the veins of the upper limbs are in very poor condition or inaccessible
- intercurrent disease leading to deterioration in general health.

Maintenance Therapy

Once iron depletion has been achieved, the aim is to prevent re-accumulation. The advocated standard practice is to maintain the serum ferritin at 50–100 µg/L. This is usually achieved with 3–6 months of phlebotomy (41).
After therapeutic phlebotomy, some patients may not show re-accumulation of iron at the expected rate. Some are taking proton pump inhibitors, which have been reported to be associated with reduced iron absorption and a reduced requirement for phlebotomy (42,43). Others may be on prescribed non-steroidal anti-inflammatory drugs. However, particularly in older patients, it is necessary to be alert to conditions that may lead to iron loss, such as peptic ulcers, colonic disease, and hematuria, which will need appropriate investigation (41). If asymptomatic C282Y/H63D compound heterozygotes are detected, recommendations regarding monitoring of iron indices are more controversial (10). The fact that individuals with this genotype may go on to exhibit a mild-to-moderate iron overload phenotype, normally associated with other comorbidity factors such as alcohol abuse or metabolic syndrome (2,28) suggest referral to a specialist for monitoring of iron indices and lifestyle habits.

Monitoring Record

A monitoring record should be completed for each patient. It is recommended that:

1. the patient have their own record book so they remain involved with their care;
2. the phlebotomy clinic/GP has a record booklet.

See the Model of Care for Therapeutic Phlebotomy for further details.

Response to Phlebotomy

The response to phlebotomy treatment depends on the presenting symptoms and the stage of the condition at the time of diagnosis. Good response is found in patients with symptoms of fatigue, skin pigmentation and abdominal pain; variable response is found in patients with symptoms of cardiomyopathy, diabetes, hypogonadism; poor response is found in patients with hepatic fibrosis, arthropathy and cirrhosis (44). In some cases, hepatic fibrosis and cirrhosis show regression after phlebotomy. However, the life-threatening complications of established cirrhosis, particularly hepatocellular carcinoma (HCC), continue to be a threat to survival even after adequate phlebotomy. Therefore, patients with cirrhosis should be managed by hepatology service and continue to be screened for HCC (11).

Number of Phlebotomy sessions required

There are few studies documenting the number of phlebotomy sessions a patient may require during the initial 'de-ironing' phase and maintenance phase. McDonnel et al (45)

reported that an average of 33.9 venesections were required during the de-ironing phase in a study of over 2000 American HH patients. Another American study reported that a median of 20 weekly or biweekly phlebotomies were performed to reach target levels (46).
A NZ study reported that on average 4 and 3 venesections for males and females respectively per year were required during the maintenance phase. When comparing C282Y homozygotes and Compound Heterozygotes (C282Y/H63D) 4 and 3.3 venesections respectively per year were needed (47).

Alternative Treatments for Therapeutic Phlebotomy

Any patients who cannot undergo phlebotomy (contraindicated) should be referred to gastroenterology/hepatology/haematology for management. There are alternative treatments but these are not widely available in Ireland:

- **Iron chelation:** Currently, the only routinely available alternative to phlebotomy is iron chelation, which is more costly and has more side effects. In iron chelation with desferrioxamine ferric ions are bound into ferrioxamine complex and eliminated from the body via the urine. Side effects include gastrointestinal symptoms, dizziness, visual and auditory impairments, muscle cramps, tachycardia, and thrombopenia. Experts recommend chelation with desferrioxamine only when phlebotomy is contraindicated—for example, when venous access cannot be obtained and in patients with circulatory problems (such as heart failure or anaemia) (12).
  The AASLD guidelines (11) recommend: Iron chelation with either deferoxamine mesylate or deferasirox is recommended in iron overloaded patients with dyserythropoietic syndromes or chronic hemolytic anaemia. (Grade 1A).
- **Therapeutic erythrocytapheresis:** Therapeutic erythrocytapheresis is the removal of erythrocytes rather than whole blood. It uses a cell separator that extracts a larger volume of red blood cells in a single pass than does phlebotomy. Preliminary results show that erthyrocytapheresis leads to fourfold reduction of phlebotomy sessions. More than twice as much iron can be removed per session and side effects are reduced. It is suitable for patients with no anaemia or heart failure and could become an alternative to phlebotomy in patients with poor compliance (36,48). Phlebotomy is cheaper and thus should be first line therapy. A survey undertaken by the EFAPH in 2010 reported that cell apheresis was available as an alternative treatment to phlebotomy in Germany, France, Hungary, Norway and Belgium (49). The efficacy, speed, tolerability, and more favourable schedule of erythorocytapheresis program facilitates treatment of HH.

Erythrocytopheresis is currently being used for blood donations in some countries, commonly referred to as 'Double Red Cell Apheresis'. Typically two packed red blood cell units are

collected from a single donor in an isovolaemic manner, with saline infusions replacing the red blood cell volume lost. Donors must have a slightly higher qualifying haemoglobin, but this approach can reduce the frequency of visits by half while still accomplishing the same pace of iron removal (40).

5.2. DIETARY MANAGEMENT FOR HAEMOCHROMATOSIS

The goal of dietary management for patients with Hereditary Haemochromatosis is to eat a balanced, nutritious diet without excessive intake of fortified or supplemental iron (1,2,11,31). There is little published research that dietary interventions and avoidance of dietary iron has a beneficial effect on patients who are undergoing phlebotomy (2). This is because the amount of iron that can be reduced on a low-iron diet (2-4mg per day) is negligible compared to that removed by phlebotomy (250mg) (11). Thus, phlebotomy remains the treatment of choice (1,2,11,31).

The following dietary advice is recommended:

- **Alcohol is a hepatotoxin and its consumption should be kept to a minimum.** Abstinence is not required unless there are other indications such as established cirrhosis (31,50). Moderate to heavy alcohol consumption increases the risk of cirrhosis by 10% in patients with HH (51) and may accelerate disease progression.
  Low risk weekly alcohol guidelines for adults are (52):
  - up to 11 standard drinks spread out over one week for women, and
  - up to 17 standard drinks spread out over one week for men.

  The standard drink in Ireland is 10 grams of pure alcohol which is equivalent to a pub measure of spirits (35.5ml), 100 ml of wine (12.5% volume) or a half pint of normal beer (52). Please note, it has been advised that the Irish Government lower these limits following reduction of UK limits in 2016. Please check www.drinkaware.ie for up-to-date guidelines.
- Avoid supplementary iron such as iron supplements, multivitamin and mineral supplements (1,2,11,31).
- Avoid supplemental vitamin C as vitamin C (ascorbic acid) increases intestinal absorption of inorganic iron. No reason exists to discourage patients from eating fresh fruits and vegetables containing vitamin C (1,2,11,31).
- Patients with elevated body iron should avoid raw shellfish (e.g. oysters) because of the risk of *Vibrio vulnificus* (bacterial food poisoning) (11,53).
- Follow a well-balanced and varied diet, with a variety of fruits, vegetables, whole grains, low fat dairy, meat and meat alternatives.
  - Following a restrictive low iron diet could compromise intake of other essential nutrients (particularly those nutrients that are abundant in iron-rich diets such as zinc and vitamin B12).
  - Restricting consumption of organ meats (such as liver) may be warranted, as these are quite high in iron.

- Calcium and tannins inhibit iron absorption so drinking dairy products and tea with meals may inhibit dietary iron absorption. However, there are conflicting reports whether tea drinking reduces the increase in iron stores in HH patients (54,55). Consumption of tea with meals can be considered, but again therapeutic phlebotomy will likely still be necessary.

The body uses vitamin B12, folate, iron and protein to manufacture new red blood cells (56). During frequent phlebotomies, patients may become deficient in vitamin B12 and folate. Oral supplements for vitamin B12 (5 µg daily) and folate (500 µg daily) support erythropoiesis during frequent phlebotomy (23).

5.3. SPECIALIST REFERRAL

Criteria for Hospital Referral and Intervention

Patients with the following should be referred on to the acute setting i.e. Gastroenterology/Hepatology:

- Patients with SF >1000 µg/L;
- Patients with cirrhosis/advanced liver disease;
- Patients with abnormal liver function tests;
- Patients with non-HFE iron overload;
- Patients who have contraindications to phlebotomies (both permanent and transient contraindications) or who have technical difficulties with phlebotomy;
- Diagnostic dilemma;
- Patients with significant co-morbidities e.g. fatty liver disease.

Please note, the above is not obligatory criteria. If a clinician is unsure of the diagnosis or treatment of a patient specialist referral should be obtained.

5.4. ACUTE MANAGEMENT

Management of complications associated with iron overload in patients with HH are summarised in Table 7.

Table 7. Management of complications associated with iron overload in HH patients.

Cirrhotic Patients	The usual practice is that cirrhotic patients should undergo HCC surveillance **every six months** with hepatic ultrasound and serum alpha-fetoprotein measurement (2). In cirrhotic patients endoscopy should be considered to determine if varices or other evidence of portal hypertension that might require therapy are present. Testing/Management includes: • Alpha – fetoprotein and liver ultrasound six monthly; • Screening OGD for Oesophageal Varices every 2-3 years; • Ensure immune to Hepatitis A or vaccinate if not; • Vaccinate against Hep B; • Pneumovax every 5-10 years.
Diabetes	Patients on insulin for diabetes mellitus usually need to continue this after phlebotomy, although their requirement for insulin may be reduced.
Arthropathy	Arthropathy usually responds poorly to phlebotomy treatment. The arthropathy may antedate the onset of liver disease or may occur for the first time after phlebotomy therapy.
Cardiac / Haemodynamic	Phlebotomy therapy usually leads to some improvement in cardiac symptoms, cardiomegaly, and haemodynamic abnormalities.

5.5. LONG TERM MANAGEMENT

The patient should have a primary care provider (GP) who can coordinate treatment with the other specialists involved and provide patient education as to the importance of early diagnosis and lifelong treatment.

Regular follow-up visits should be scheduled with the primary care provider who should monitor for the development of the potential complications of the disease. Quarterly visits with healthcare providers may be necessary depending on the severity of the symptoms or complications. Patients with complications associated with HH should be referred to the appropriate specialties.

5.6. PROGRESSION OF HAEMOCHROMATOSIS

The AASLD practice guidelines states that HH evolves over a series of stages (11).

Table 8. Different Stages and Progression of Haemochromatosis

Stage 1	Those patients with the genetic disorder with no increase in iron stores who have "genetic susceptibility."
Stage 2	Those patients with the genetic disorder who have phenotypic evidence of iron overload but who are without tissue or organ damage.
Stage 3	Those individuals who have the genetic disorder with iron overload and have iron deposition to the degree that tissue and organ damage occurs.

The complications of iron overload and untreated haemochromatosis include the following:

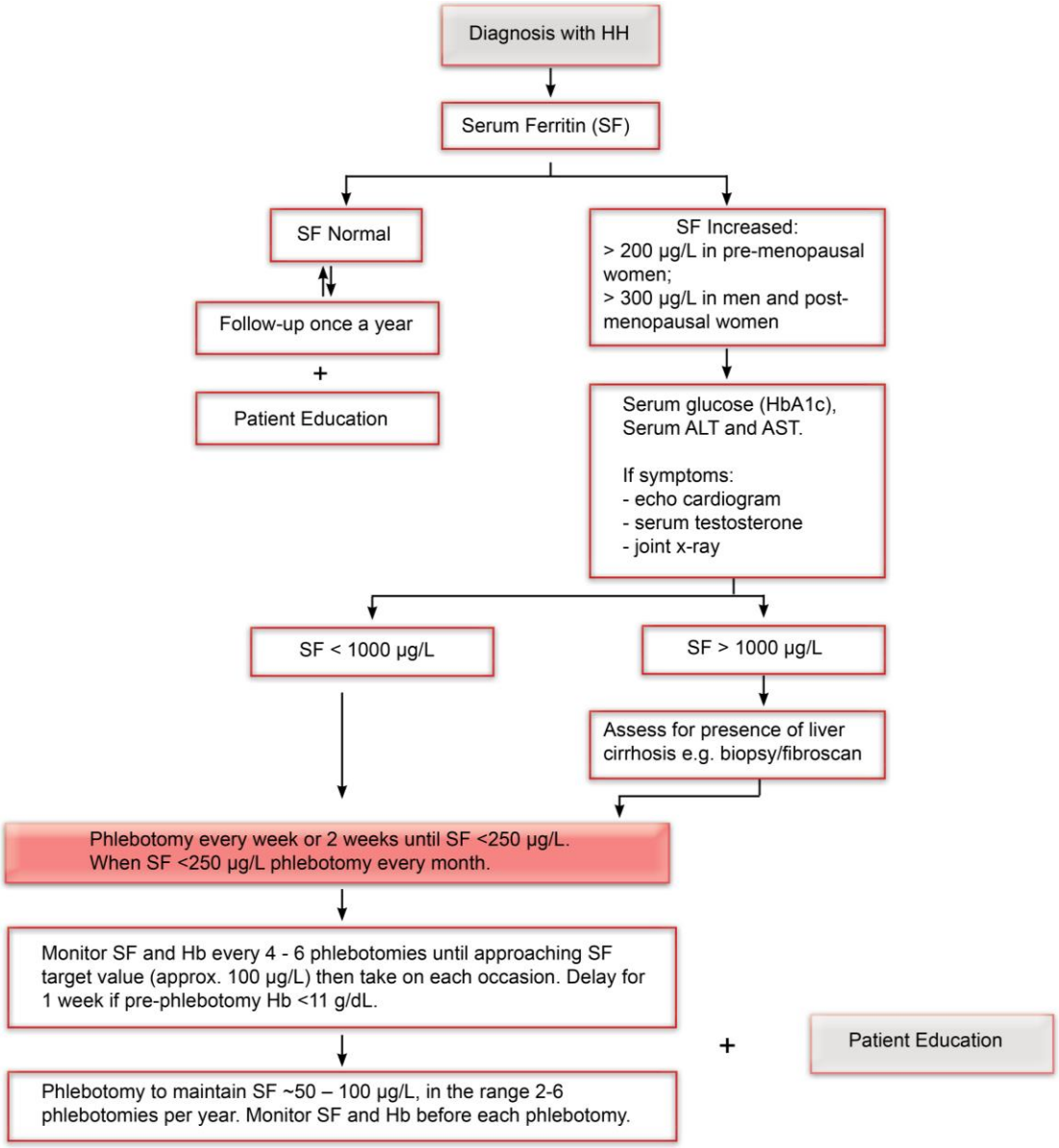
- Liver disease with fibrosis or cirrhosis, with hepatocellular carcinoma occurring in up to a third of cirrhotic patients
- Arthritis
- Gonadal failure
- Diabetes mellitus
- Cardiac failure and arrhythmias

5.7. PROGNOSIS

The prognosis of haemochromatosis has been significantly improved by phlebotomy therapy. Non-cirrhotic patients diagnosed and treated early have a normal life expectancy compared to age and sex-matched controls, provided they continue treatment. Life expectancy is reduced in those who present with cirrhosis or diabetes mellitus. Patients with cirrhosis have a risk of death due to hepatocellular carcinoma even when complete iron depletion is achieved (31).

5.8. SUMMARY OF TREATMENT

Algorithm for Management of Patients with HH (based on EASL guidelines (2)***).***



Patients with complications associated with HH should be referred to the appropriate specialties.

6. PATIENT EDUCATION

6.1. PATIENT EDUCATION

Patients with HH should be provided with education surrounding Hereditary Hemochromatosis. This is to be given by the clinician who is in charge of the long term management of the patient or by the phlebotomy centre where the patient is receiving treatment. A survey undertook by the EFAPH in 2014 identified the general practitioner as the preferred information source for patients with hereditary haemochromatosis (57). The education should include the following (58) :

- Ascertain what the patient already knows about haemochromatosis.
- Explain the symptoms and diagnosis of hereditary haemochromatosis (explain to the patient what to expect with regard to blood testing and genetic testing).
- Explain the hereditary nature of this condition and the need for family members to be tested.
- Explain the clinical progression of HH and of the health conditions related to iron overload (liver damage, liver cancer, heart disease, arthritis, diabetes, sexual impotence).
- Explain the management of hereditary haemochromatosis including therapeutic phlebotomy procedure and duration, venepuncture sites, goals and whether it is possible to donate blood removed through phlebotomy.
- Explain the importance of compliance with treatment and the need for life-long management/review for a symptom free life.
- Explanation of test results, especially HFE genotype, transferrin saturation and serum ferritin.
- Give dietary advice to the patient and his or her family (especially the effect of alcohol consumption).
- Smoking is ill-advised for everyone. Support should be offered to patients who smoke. A wide range of services available to help smokers to quit, see http://www.hse.ie/eng/about/Who/TobaccoControl/cessation/.
- Advise the patient to report any allergies and physiological intolerance to treatment. Inform the patient of the potential complications associated with haemochromatosis.
- Repeat information as indicated and allow an opportunity for the patient to ask questions.
- Document patient teaching.

Patient and GP Education Resource is attached at the end of this document.

For further education materials, patients can access a patient information booklet from:

- The Irish Haemochromatosis Association http://www.haemochromatosis-ir.com/
- The UK Haemochromatosis Society http://haemochromatosis.org.uk/support/handbook/
- Haemochromatosis Australia http://haemochromatosis.org.au/

7. GOVERNANCE

7.1. INTRODUCTION

This paper will describe the governance arrangements which may apply at any point in the patient journey. It will necessarily reflect the choices of the patient at certain points in the journey.
(Standard 1.1. The planning, design and delivery of services are informed by service users' needs and preferences.)
It is also based on an implicit hierarchy of expertise (with associated obligations) and principles of safe delegation and handover. It is important at any handover that it is clear where responsibility/accountability rests.

7.2. GOVERNANCE AND ACCOUNTABILITY PRINCIPLES

Standard 2.4 states:
An identified healthcare professional has overall responsibility and accountability for a service user's care during an episode of care.
This is distinct from the clinical governance of a facility or service, in that it is particular to the individual patient, although the same individual can be responsible for both in many situations, particularly in less complex environments.
The Irish Medical Council Guide to Professional Conduct and Ethics for Registered Medical Practitioners 8th Edition 2016 provides useful guidance on this point:

Delegation and referral

22.1 'Delegation' involves you asking another health care professional to provide care on your behalf.
22.2 'Referral' involves you sending a patient to another doctor or healthcare professional to get an opinion or treatment. Referral usually involves the transfer (in part) of responsibility for the patient's care, usually for a set time and a particular purpose, such as care that is outside your area of expertise.
22.3 When you delegate or refer you must give sufficient information about the patient and their treatment to the clinicians continuing the care of the patient. You should take reasonable steps to make sure that the person to whom you delegate or refer has the qualifications, experience, knowledge and skills to give the care needed.

23 Handover

23.1 Handover is the transfer of professional responsibility and accountability for some or all aspects of the care of a patient, or group of patients, to another person or professional group on a temporary or permanent basis. You will hand over care when you change shift, refer a patient to secondary care or other health professionals, or when your patient returns to the care of their GP. Handovers may take place between teams and/or between individuals.
23.2 When you hand over care for a patient to another healthcare professional, team and/or institution, you should check that they understand and accept responsibility for the patient's care. You should pass on all relevant information about the patient and the patient's care.

38 Referral of patients

38.1 It is in the best interests of the patient that the overall management of their health is under the supervision and guidance of a general practitioner.
38.2 If you consider that it is in the best interests of the patient to be referred for specialist opinion, you should consider relevant professional guidelines and refer your patient to a specialist who is competent and appropriately skilled to deal with the particular patient. (See also paragraph 23.)
38.3 Normally, consultants will see patients following referral from their general practitioner, another consultant or treating doctor.
It is also helpful to elaborate the following issues related to accountability and delegation:
All practitioners must ensure that they perform competently and that they don't work beyond their level of competence. When dealing with a matter which is beyond their competence they should refer appropriately.

To be accountable, practitioners must:

- have the ability to perform the activity or intervention;
- accept responsibility for doing the activity;
- have the authority to perform the activity;
- when delegating an activity, they must ensure that it has been appropriately delegated;
- they are responsible that they only delegate tasks and duties that are within the other person's competence;
- make sure that everyone they delegate tasks to is adequately supervised and supported;
- confirm that the outcome of any task they have delegated to someone else meets the required standard.

7.3. APPLYING THESE PRINCIPLES TO THE MANAGEMENT OF HAEMOCHROMATOSIS

Diagnosis and assessment

The patient enters the pathway at the point of diagnosis: as Haemochromatosis has a range of presentations this could be almost any physician depending on the presenting condition. The presenting physician is responsible at this point for arranging appropriate diagnostic assessment of the patient, this will typically be a General Practitioner. This can be performed by the physician themselves, delegated to a subordinate (where responsibility remains with the delegating physician) or referred to a more appropriate specialist. Once the referral is accepted by the specialist there is an associated transfer of accountability, and it is assumed that the specialist will normally accept this responsibility unless they feel that the referral is inappropriate or that for some reason they cannot discharge the responsibility and there is a more appropriate alternative available. This requires clinical judgement informed by clinical guidelines and available options for the patient. It is appropriate to involve the patient in these decisions.

Phlebotomy

The process of phlebotomy can be delivered in several different environments, and each service will have a clinical governance structure which will be responsible for ensuring that the service is delivered safely and effectively. Separately to this any patient undergoing therapeutic phlebotomy will have that treatment prescribed by an identified prescriber who will normally be their treating physician (i.e. GP), based on the diagnostic pathway. While phlebotomy can be delegated to be performed according to an agreed protocol the prescribing physician remains responsible for ensuring that they are satisfied that the person delegated has the necessary skills and competences, and that appropriate communication links and protocols are established. The Prescriber is responsible for monitoring the patient's management with reference to the appropriate guidelines and with input from others involved in providing phlebotomy or other care. Parts of this process can be delegated in appropriate circumstances.

Screening of family members

It would normally be expected that the patient would communicate the need for first degree relatives (siblings, offspring and parents) to be screened, and responsibility for this rests with the patient. The physician responsible for confirming the diagnosis should encourage and assist them in providing necessary information to the family, and the doctors

of the family members. It is expected that screening would typically be initiated by the family members and arranged by or through the family member's own General Practitioner.

Follow up

A specialist may discharge the patient back to the GP with agreed transfer of accountability in line with Medical Council Guidelines where the specialist is satisfied that this is appropriate and the referring source is willing and able to discharge the responsibility. Shared care arrangements, formal or informal, may be appropriate in some circumstances, but it is important that all involved are clear about who has overall accountability and responsibility for the patients care, and what aspects of care are delegated.

7.4. ROLES AND RESPONSIBLITIES

1. The **General Practitioner** is responsible for the management of Hereditary Haemochromatosis patients in the community. The role of the GP in HH will include the following:

- confirmation of diagnosis;
- assessment of complications/comorbidities;
- appropriate specialist referral;
- development of a treatment plan and schedule of therapeutic phlebotomy;
- refer patient for Therapeutic Phlebotomy or undertake Phlebotomy as per policies outlined in Model of Care for Therapeutic Phlebotomy;
- liaise with the phlebotomy clinic where the patient is receiving treatment;
- planned follow-up of the patient over their lifetime, dependant on clinical need;
- provide education about Hereditary Haemochromatosis and its management;
- discuss the importance of family screening for first degree relatives when an individual has been diagnosed with HH.

2. *The **Consultant Gastroenterologist/Hepatologist/Haematologist (i.e. specialist)** will be responsible for a minority of patients who have/are referred due to the following:*

- patients with SF >1000 µg/L;
- patients with cirrhosis/advanced liver disease;
- patients with abnormal liver function tests;
- patients with non-HFE iron overload;
- patients who have contraindications to phlebotomies (both permanent and transient contraindications) or who have technical difficulties with phlebotomy;

- diagnostic dilemma
- patients with significant co-morbidities e.g. fatty liver disease.

Please note the above is not obligatory criteria. If a clinician is unsure of the diagnosis or treatment specialist referral should be obtained.

3. The **lead of each phlebotomy clinic** has overall accountability and responsibility for the day to day management, operation, quality and safety of the phlebotomy service. The lead should have easy and timely access to the patient's clinical manager i.e. the GP or Consultant to discuss treatment plans and patient progress. Please refer to the guidelines MOC for Therapeutic Phlebotomy for recommendations for standard operating procedures and policies.

4. **Phlebotomist/Nurse:** It is the responsibility of the phlebotomist/nurse to comply with the guidelines in this document and the associated document, MOC for Therapeutic Phlebotomy which details the competency requirements and responsibility of clinicians delivering phlebotomy.

5. **Clerical Officers/Administration staff** to help with administrative demands of service i.e. ordering charts, filing and paperwork, coding sheet, phone calls and making appointments

6. **Irish Blood Transfusion Service:** The IBTS operates within its own governance structure. Its involvement with the phlebotomy programme includes:

- facilitating the identification of potential donors with HH;
- provision of phlebotomy services for haemochromatosis patients who choose to donate for some or all of their treatments;
- completing patients record/monitoring card;
- sharing expertise around phlebotomy.

In conclusion, it is the responsibility of each health care professional involved in patient care to comply with the guidelines in this document and the associated document, Model of Care for Therapeutic Phlebotomy.

8. FUTURE OF HH RESEARCH AND MANAGEMENT IN IRELAND

8.1. DEVELOPMENT OF A PATIENT REGISTER

It is proposed that all patients with Hereditary Haemochromatosis should be input on a national register. This could be used to determine clinical penetrance of the disease and allow for a central register for patient details and phlebotomy schedules to be accessed allowing patients to get phlebotomies anywhere in the country.
A report published by Orphanet in 2016 on the Rare Disease Registries found that there is only one register for patients with HH in Europe and it is in Languedoc Roussillon Region, France (59). The report states that patient registries and databases constitute key instruments to develop clinical research in the field of rare diseases, to improve patient care and healthcare planning. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research. They are vital to assess the feasibility of clinical trials, to facilitate the planning of appropriate clinical trials and to support the enrolment of patients. A 2010 study using this registry characterised the history of HH, particularly for the most severely affected patients, determined the prevalence of symptomatic C282Y homozygotes in the region and the clinical penetrance, which was found to be not negligible (60).

If a national dataset is established, it could be actively monitored to identify and flag patients who appear to be poorly controlled, and those who may be under-treated or over-treated. This process could also flag providers who may be significantly deviating from expected performance standards for further inquiry.

8.2. APP DEVELOPMENT

The patient register could be developed along with an app. Two successful international examples include:

- In Australia, a national haemochromatosis patient's registry in collaboration with High Ferritin app (HFa) (https://highferritin.transfusion.com.au/) was developed by Australian Red Cross Blood Services. It is accessible to the patients, their doctors and Red Cross Blood Collection Services 24 hours a day anywhere in the country and allows the patients to donate the blood collected for therapeutic purposes at any affiliated blood collection centre in the country. Patients automatically get a

message either by email or text message after their blood results have been reviewed by their doctor and they are required to go for phlebotomies.

- In Canada, a free app (Iron Tracker) was developed by two Canadian Universities in coordination with the Canadian Hemochromatosis Society. It provides patients a single place where treatment and life-long progress can be tracked, combining appointment management with tracking and visualisation of body haemoglobin and ferritin values, providing a clear visualisation of this data to better understand and share progress with friends, family and physicians. The app also tracks phlebotomy appointments and details, helping patients manage their lifestyle.

8.3. STUDIES TO EXAMINE THE PREVALENCE OF HH IN IRELAND

Due to Ireland having the highest rates of HH in the world, a report from a Working Group set up by the Tánaiste in March 2006 to examine the nature and extent of haemochromatosis in Ireland (9) recommended:

'Funding must be prioritised to develop a HH screening programme. Information obtained from this programme will provide essential guidance to policy makers in structuring a countrywide programme for HH service development.'

They stated that:

'An Irish study, which screened 330 people for HH, reported high sensitivity using a TS result above 45% as indicative of a positive test, i.e. highly suggestive of haemochromatosis (60). Phenotypic screening of the general population using these standard iron indices with genotypic confirmation of HH in those with elevated biochemical markers has been reported to be a cost-effective strategy for identification of C282Y homozygotes in other countries. This strategy has a high predictive value even when it was assumed that fewer than 20% of the cases would develop life-threatening complications of the disease. In Ireland, there is no published large-scale study of the phenotypic expression (assessment of iron levels) of the C282Y mutation. Such a study would be useful in determining the necessity for nationwide population screening.

The primary objective of a screening proposal would be to determine the prevalence of HH homozygosity in Ireland by screening 10,000 subjects, and to establish a phenotype/ genotype correlation in affected persons. The establishment of a large cohort of HH patients with different levels of clinical expression provides a unique opportunity for translational research into the role of genetic modifiers of iron loading in disease expression. These data will lead directly to the development of an Irish model of clinical care for patients with HH.

The structure of the proposal coupled to stakeholder involvement will lead to the development and implementation of guidelines for the diagnosis and treatment of this common disease at primary, secondary and tertiary levels through national networks thereby providing equity of access to care for all persons.'

A screening project should be considered in the future.

9. INTERDEPENDENCIES AND CONSULTATION

The successful implementation of this model of care requires the coordination among the following stakeholders:

- HSE (Acute Care and Primary Care);
- Irish Blood Transfusion Service (IBTS);
- Irish Haemochromatosis Association (IHA).

9.1. IRISH HAEMOCHROMATOSIS ASSOCIATION (IHA)

The IHA is a voluntary organisation which aims to provide support and information for those suffering with haemochromatosis and related disorders, to facilitate networking among members, and to encourage screening of members' extended families through: (61)

- production of a newsletter, brochures, and other media that provide information about and raise awareness of Haemochromatosis;
- formation of a membership bank;
- education of the general public and members of the medical profession about haemochromatosis;
- information gathering to advance knowledge of the disorder;
- the promotion and development of relationships with other voluntary agencies and with those involved in the medical field in order to advance the knowledge and treatment of haemochromatosis;
- fundraising to assist the organisation in its objectives.

The IHA have done a significant job in raising awareness of Haemochromatosis in Ireland.

9.2. CONSULTATION AND INVOLVEMENT OF SERVICE USERS

The Hereditary Hemochromatosis Working Group has representation from the IHA. The Working Group has taken note of a survey of Hemochromatosis patients to determine from a patients perspective: a) what problems are currently experienced regarding access to phlebotomy and b) what factors might be considered regarding improvement of access to phlebotomy. The results were submitted in June 2015.

10. APPENDICES

APPENDIX 1. ACKNOWLEDGEMENTS

Working Group

Dr. Colm Henry	National Clinical Advisor and Group Lead Acute Hospitals
Dr John Lee	Consultant Gastroenterologist
Dr. Clifford Kiat	Gastroenterologist
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Noreen Curtain	CIT OPAT Programme Manager
Dr. Joe Clarke	GP, GP Minor Surgery Research Network Project
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Aisling Phelan	RD, Project Manager

Additional Thank You to:

Dr. David Barton	Chief Scientist & Adjunct Associate Professor Molecular Genetics Laboratory Department of Clinical Genetics Our Lady's Children's Hospital
Dr. Gerard Boran	Consultant Chemical Pathologist
Joe Ryan	Acting Head of the Programme for Health Service Improvement

APPENDIX 2. PHLEBOTOMY DISCHARGES

No. of Discharges in 2014 of patients with ANY DIAGNOSIS OF HAEMACHROMATOSIS (ICD-10 E83.1 - Disorders of iron metabolism Haemochromatosis) with a phlebotomy procedure (ICD-10 Code 1375700 - Therapeutic Phlebotomy).

*Please note, this only contains inpatient and day case data. Outpatients are not included e.g. patients treated in St. James Hospital, Dublin and St. Luke's Hospital, Kilkenny are not included here. St. Luke's Hospital has moved to a Day Services Unit and discharges will now be captured on HIPE.

HOSPITAL NAMES	No. of Discharges
UCH, Galway (404)	3345
Louth County, Dundalk (703)	1719
Tallaght Hospital (041)	1687
Tullamore Regional (501)	1570
St. Joseph's Raheny (044)	1472
Sligo General (602)	986
Mater Misericordiae (005)	983
St. Vincent's University, Elm Park (007)	834
Connolly (022)	781
Portiuncula, Ballinasloe (403)	558
Wexford General (103)	518
Letterkenny General (601)	494
Mayo General (405)	478
St. John's, Limerick (305)	441
Portlaoise Regional (506)	434
Monaghan General (704)	428
Ennis Regional (307)	423
Nenagh Regional (308)	423
St. Michael's, Dun Laoghaire (023)	407
Naas General (004)	391
Cavan General (702)	354
South Infirmary - Victoria, Cork (206)	324
Roscommon County (401)	318
Mercy University, Cork (203)	245
Waterford Regional (100)	205
Mallow General (207)	190
Mullingar Regional (503)	165
Our Lady's, Navan (705)	143
Cork University (235)	83
Beaumont (037)	72
Limerick Regional (303)	22
Our Lady of Lourdes, Drogheda (701)	5
Tralee General (236)	4
Bantry (202)	1
TOTAL	20503

NOTE: THIS IS IN-PATIENT AND DAY CASE ONLY. NO OUT-PATIENT DATA RECORDED.

APPENDIX 3. DATA PROTECTION, INSURANCE AND GENETIC TESTING

Genetic test results are personal data. The following is law under the Disability Act of 2005:

- Informed consent of data subject required to processing of genetic data;
- Processing of genetic data is prohibited in relation to insurance policies, pensions, and mortgages;
- Processing of genetic data is subject to Data Protection Commissioner prior approval in relation to employment.

A report on the Code of Practice on Data Protection for the Insurance Sector (62) from the Data Protection Commissioner states that:

'The Disability Act 2005 provides that the processing of genetic data in relation to insurance, life insurance, health insurance or health-related insurance, an occupational pension, a retirement annuity contract or any other pension arrangement is prohibited.

An Insurer will not request an applicant to have a genetic test. Application or other forms which ask health questions of an individual or his/her doctor must not include any question about genetic tests. Forms which ask health questions directly of the individual must include a form of words bringing to his/her attention the fact that he/she should not disclose a genetic test result.

Each request to a person's GP, an independent doctor or a claims visitor to assess and/or examine an individual on an insurer's behalf which may involve the taking of a health history other than by way 10 of completing a standard medical examination report form must include a form of words bringing to the doctor's attention the fact that he/she should not include any genetic test result in his/her report.

Despite the inclusion of the above wordings on relevant insurance forms it is possible that applicants, claimants or doctors will in some instances include genetic test results in such forms.

In the event of a genetic test result coming into the possession of an insurer, the genetic test result must be ignored and not taken account of by the insurer in any way whatsoever. This applies both to positive and negative test results.

Genetic test results coming into an insurer's possession in this way are likely to be included in the body of an application form or medical report. Ideally the genetic test results should be deleted from the paper and/or electronic file. Where this is not practical, a note should be made on the file confirming that the genetic test result has been ignored in accordance with the Disability Act 2005.'

Insurance and Genetic Testing

Under the provisions of Part 4 of the Disability Act 2005, an insurer cannot request, take into account or process the results of genetic tests. This applies to both positive and negative tests. Under the legislation, an insurer may not take into account a negative test result even if you ask the insurer to do so.
However this exception does not change the applicant's legal obligation to provide the insurance company with full details of any:

- symptoms experienced;
- non-genetic laboratory tests or investigations;
- treatment;
- family history (63).

Where a blood test is normal and sufficient time has elapsed since diagnosis to establish that the condition is well controlled, an individual should generally be able to obtain life cover (which includes mortgage protection cover) at the standard premium. However, if there are complicating factors, e.g. there is a high iron level or organ damage, an extra premium may be applied and there may also be a small number of cases where the individual is uninsurable. For patients with HH, the individual's current state of health at the time of the insurance application is the key issue. Where somebody is diagnosed with a condition or where his/her health deteriorates after taking out a policy, this will have no impact on any existing policies that he/she may have (as long as he/she has answered all questions fully at the time of applying for the policy and continues to pay the premiums due) (9).

APPENDIX 4. QUICK REFERENCE TABLE FOR CONFIRMING THE DIAGNOSIS OF HEREDITARY HAEMOCHROMATOSIS AND THE MANAGEMENT OF A PATIENT WITH DIFFERENT IRON STUDY RESULTS, ADAPTED FROM THE BRITISH COMMITTEE FOR STANDARDS IN HAEMATOLOGY 2010 (35).

Confirming the diagnosis of HH in a patient with evidence of iron overload but no evidence of liver damage

No hepatomegaly, AST activity normal, serum ferritin concentration is >200 µg/L in males and >300 µg/L in pre-menopausal women and < 1000 µg/L:

1. In most cases genotyping will confirm the diagnosis of genetic haemochromatosis. Approximately 90% of patients have the genotype C282Y +/+, 5% have C282Y +/-, H63D +/-.
2. Commence quantitative phlebotomy. Removal of more than 4 g iron demonstrates that body iron stores are compatible with genetic haemochromatosis.

Confirming the diagnosis of HH in a patient with evidence of liver damage

Serum ferritin concentration is >200 µg/L in males and >300 µg/L in pre-menopausal women, AST activity is above normal or there is hepatomegaly:

1. Genotyping
2. Carry out liver biopsy/fibroscan to show hepatic architecture (normal/fibrosis/cirrhosis).The presence of cirrhosis has significant prognostic implications and will affect management
3. Carry out histological grading of iron concentration (Perl's stain). Increased stainable iron in hepatic parenchymal cells confirms iron loading.

Confirming the diagnosis of HH in a patient with only a raised transferrin saturation

If the fasting transferrin saturation is raised but serum ferritin and AST levels are normal:

1. In most cases genotyping will confirm genetic haemochromatosis
2. If the genotype is that of homozygous haemochromatosis, transferrin saturation and serum ferritin should be monitored at yearly intervals. If serum ferritin becomes elevated, phlebotomy should be started
3. If the genotype is normal the serum ferritin concentration should be monitored at yearly intervals.

Investigation of patients with evidence of iron accumulation but negative for HFE mutations

1. Search for other causes of elevated transferrin saturation or serum ferritin concentration, e.g. fatty liver, alcoholic liver disease, haematological disease.
2. Consider referral to specialist centre.
3. Measure liver iron concentration and calculate the hepatic iron index: µmol/g dry weight of liver divided by age (years) at time of biopsy (> 1.9 in homozygous genetic haemochromatosis with iron overload). In the absence of the common HFE genotypes, this allows a diagnosis of parenchymal iron overload compatible with genetic haemochromatosis.

APPENDIX 5. LETTER TO BE SENT TO FIRST DEGREE RELATIVES

Only to be sent after obtaining the patient's consent.

First Degree Relatives = Adult siblings (brothers & sisters) and offspring of C282Y homozygotes. Parents of C282Y homozygotes should be screened only after a clinical decision depending on their age, sex and ferritin.

Dear Family Member,

A member of your family has been diagnosed with Hereditary Haemochromatosis.

Their genotype is _____

This is an inherited genetic condition that causes the body to absorb too much iron from food. This iron is then deposited in organs such as the liver, heart and pancreas and can cause damage over time. As you are a genetically related family member you may have inherited the altered genes that cause this disease.

Most people do not feel unwell during the early stages of the condition and cannot tell if they have the disease. Sometimes people can feel common symptoms such as fatigue and aching joints. However iron gradually builds up in your organs over time causing permanent damage. This can be prevented by the early diagnosis of the disease.

If you wish to find out if you have are predisposed to this condition you should go to your GP. Your GP will explain the condition to you, and can take have a simple blood test. The blood test is used to check your iron levels (serum ferritin and transferrin saturation) and to see if you have the same genetic condition as your family member. This is called the HFE gene test. The good news is that complications from haemochromatosis can be prevented if it is found and treated early. Testing is done on family members aged over 18 years of age as it is unusual for a person under the age of 18 to have high iron.

Iron Studies	***HFE Gene Test***
• *Fasting Transferrin Saturation* • *Fasting Serum Ferritin*	• *C282Y* • *According to local practice, H63D can be considered an optional complementary test that can be offered sequentially or simultaneously to C282Y testing*

If the test results show that you have excessive iron as well as the genetic condition you will need to begin phlebotomy treatment. This is a safe, simple and effective treatment which involves having approximately 500mL of blood taken from a vein in the arm, like donating blood. If the test results show you have normal iron but the same genetic predisposition as your family member, then you will need to have your iron levels checked every year.

Please do not ignore this letter as ***EARLY diagnosis is vital****. With proper treatment, people with haemochromatosis lead normal, healthy lives. For more information on this condition visit: https://www.hse.ie/eng/health/az/H/Haemochromatosis/*

Sincerely,

_____-

Your GP.

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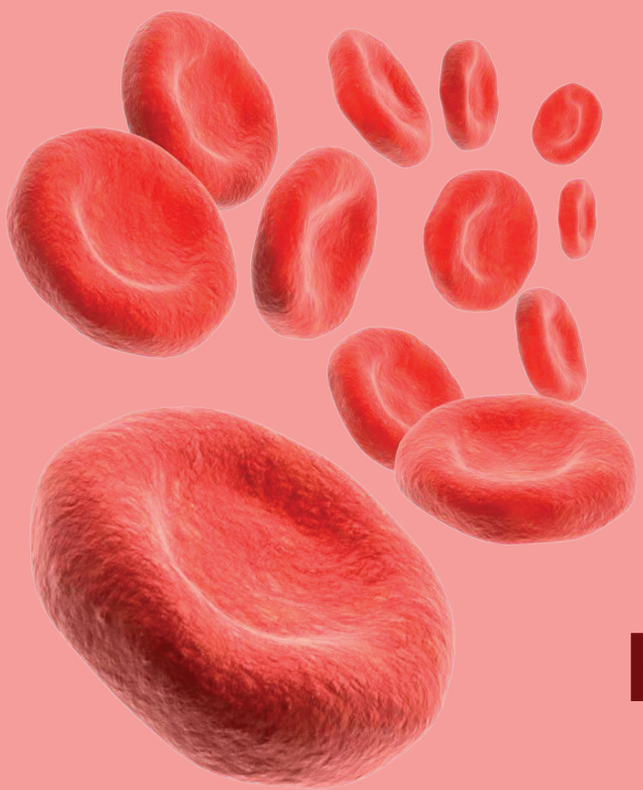


Hereditary Haemochromatosis

For GPs

What is Hereditary Haemochromatosis?

Hereditary Haemochromatosis (HH) is a common autosomal recessive disease resulting in excessive absorption of dietary iron from the intestine. Over time, excess iron accumulates in the parenchymal cells of organs including the liver, pancreas, heart and anterior pituitary causing organ damage.

HH is more common in people of Celtic or northern European decent. It is the most common genetic disease in Ireland with approximately 1 in 83 people predisposed to develop HH .

Early diagnosis and treatment of HH prevents complications and results in a normal life expectancy. Phlebotomy is a simple and effective way to both prevent and manage iron overload in patients with HH.

The Genetics of HH

Hereditary Haemochromatosis is caused by mutations in the HFE gene, mainly C282Y. The association with haemochromatosis with HFE variants other than C282Y, such as H63D, is still debated and no established consensus has been published.

Carriers (also known as heterozygotes) have one altered HFE gene and one normal HFE gene and are generally not affected by iron overload. Iron overload arises when both copies of the HFE gene are altered/mutated. Not everyone who inherits two HFE mutations will develop iron overload and fewer will develop the clinical syndrome.

The majority of patients are homozygous for the C282Y mutation in the HFE gene. The prevalence of the C282Y homozygous state in the Irish population has been estimated at 1.2% or approximately 55,000 individuals. However not all patients develop symptoms due to variable clinical penetrance.

C282Y/H63D compound heterozygosity is a risk factor for slightly higher serum iron parameters and mildly increased hepatic iron stores when in association with co-morbidity factors, for example, alcohol or metabolic syndrome.

There are several factors known to influence expression of the disease in those patients who are genetically susceptible. Women tend to have a later and less severe onset because of menstruation and pregnancy. Alcohol, a diet high in iron, obesity and hepatitis B and C increase the chance of clinical symptoms.

A blood based genetic test can be arranged to screen for the HFE mutations. HH is an adult onset disease, and testing of minors is not recommended.

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

What are the Symptoms?

Symptomatic organ involvement, when it does occur, tends to begin in middle age. No two people are alike and symptoms will vary from person to person.

The most common symptoms noticed by people with HH include:

- Fatigue, general weakness and lethargy
- Joint pain. Knuckle and first joint of the first two fingers are commonly affected
- Abdominal pain
- Sexual dysfunction
- Discoloration of or bronzing of skin
- Mood swings and irritability

The early biochemical signs of HH tend to be:

- Increased serum ferritin and transferrin saturation
- Abnormal liver function tests (LFTs)
- Hepatomegaly (enlarged liver)

Symptoms are often attributed to other causes, leading to delay in diagnosis. Combinations of the symptoms of HH can and should lead to early diagnosis.

If not treated early, people with HH can develop diabetes mellitus, cirrhosis, cardiac problems and hepatocellular carcinoma.

Consider Testing For HH in:

- Patients with liver disease of unknown cause, including patients with suspected alcoholic liver disease.
- Family members of HH patients.
- Chronic unexplained fatigue, weakness and abdominal pain.
- Asymptomatic patients with incidental elevated LFT, ferritin or hepatomegaly.
- Early onset arthralgia (joint pain), atypical arthropathy.
- Early onset male impotency, early menopause and loss of libido in women.
- Early onset arrhythmias and cardiomyopathy.
- Unexplained increasing skin pigmentation or ‘permanent tan’.
- Type 2 diabetes mellitus, especially those diagnosed at an early age, with elevated LFT, hepatomegaly, early-onset sexual dysfunction or abnormal iron markers.

Diagnosis of HH

The clinical diagnosis of hereditary haemochromatosis is C282Y homozygosity and increased body iron stores with or without clinical symptoms.
Therefore, HH is diagnosed in terms of phenotype (raised serum ferritin and transferrin saturation) and genotype, and is not made by identification of mutated genes alone.

For practical clinical purposes, C282Y/H63D compound heterozygotes and H63D homozygotes are not classified as HFE-associated HH (following the most recent EASL guidelines), and it is recommended that in patients with these genotypes and iron overload, other causes of hyperferritinemia should first be investigated. These patients may be at-risk of developing mild to moderate iron overload in association with comorbid factors and may be appropriate for therapeutic phlebotomy.

See the table overleaf for more details on the interpretation of the genetic result and the risk of developing iron overload.

If an individual has raised SF and TS and is homozygous for C282Y then the diagnosis of HH is made.

What are the tests?

Iron Studies

Both fasting transferrin saturation (TS) and serum ferritin (SF) are required as patients in the early stages of clinical disease can have normal SF, but raised TS. In addition, SF is an acute phase protein which can be raised during illness.

Serum Ferritin
SF reflects body iron stores but, as an acute phase reactant, can be elevated non-specifically on occasions (e.g. through alcohol consumption, chronic inflammation and other liver diseases).

A SF of > 200 µg/L in pre-menopausal women and > 300 µg/L in men and post-menopausal women suggests that the patient may be iron overloaded. This should prompt a test for fasting TS.

Patients with a SF >1000 µg/L should have a referral to gastroenterology/hepatology at the same time the blood test is sent for genetic testing. This is because as SF >1000 µg/L places the individual at increased risk of severe HH related morbidity such as liver cirrhosis and a liver biopsy/fibroscan needs to be done.

Transferrin Saturation
Fasting transferrin saturation of >45% is strongly suggestive of HH and should prompt a test for HFE gene testing. Transferrin saturation is the proportion of the iron transport protein transferrin that is saturated with iron. An increased TS reflects increased absorption of iron – the underlying biological defect of this condition.

HFE Genetic Testing

If fasting transferrin saturation is >45%, HFE genetic testing should be done. Laboratories should test for C282Y and, according to local practice, H63D can be considered an optional complementary test that can be offered sequentially or simultaneously to C282Y testing.
If the patient is negative for the HFE mutations, further investigations for hyperferritinemia should be done.

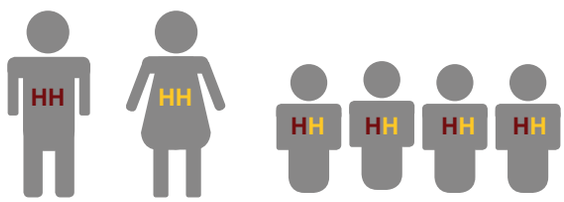
The HFE gene test is performed once, whereas iron studies are performed every time an assessment of current iron overload is required.

Genotype (Prevalence in Population)	Interpretation of result and risk of developing Iron Overload
Homozygous C282Y (1 in 83)	Diagnosis of Hereditary Haemochromatosis is made in the presence of iron overload. Are at risk of developing HH (i.e. not everyone with this genotype will develop HH), therefore are at risk of developing significant iron overload.
Compound Heterozygous C282Y/H63D (1 in 60)	Excludes the diagnosis of the most common form of Hereditary Haemochromatosis, genotype consistent with mild to moderate iron overload. May be at-risk of developing mild to moderate iron overload in association with other factors (e.g. alcohol consumption, fatty liver disease and/or metabolic syndrome) and may be considered for treatment via phlebotomy.
Heterozygous C282Y (1 in 5)	At no increased risk of developing Hereditary Haemochromatosis associated iron overload. Is a carrier of Hereditary Haemochromatosis. If iron overloaded, other causes of iron overload should be considered.
Heterozygous H63D	At no increased risk of developing HH associated iron overload. If iron overloaded, other causes of iron overload should be considered.
Homozygous H63D	At no increased risk of developing HH associated iron overload. If iron overloaded, other causes of iron overload should be considered.
Normal Genotype	At no increased risk of developing HH associated iron overload. If iron overloaded, other causes of iron overload should be considered.

Inheritance of Haemochromatosis

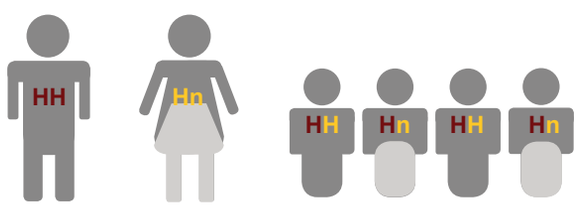
Each person has 2 copies of the HFE gene, one copy inherited from their mother and one from their father. Each copy will either be normal (n) or have the C282Y mutation (H). Therefore each person has 3 possible combinations for their HFE gene.

1.



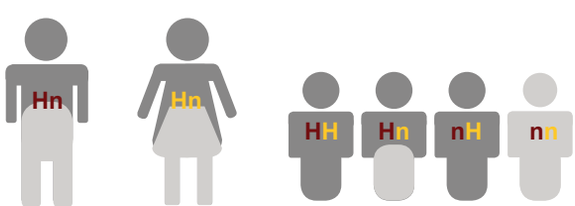
Homozygous for C282Y | **Homozygous for C282Y** | **100% chance Homozygous for C282Y**

2.



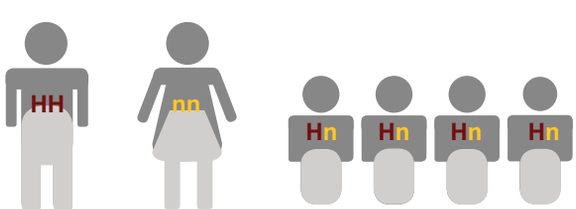
Homozygous for C282Y | **Heterozygous Carrier** | **50% chance - Homozygous**
50% Chance - Heterozygous carrier

3.



Heterozygous Carrier | **Heterozygous Carrier** | **25% chance - Homozygous**
50% Chance - Carrier
25% chance - Normal

4.



Homozygous for C282Y | **Normal Genotype** | **100% chance carriers**

Management

Family Screening

Genetic testing of adult siblings and offspring of a patient diagnosed with HH (C282Y homozygous) is recommended. Parents of C282Y homozygotes should be screened after a clinical decision depending on their age, sex and ferritin. If patients with HH are worried about their children, it is useful to perform genetic testing on the other parent to predict whether the children will need to be considered for genetic testing.

Work Up

If SF is elevated, initial evaluation should include fasting blood glucose, HbA1c, serum AST, and ALT activity.

Patients should be referred onto a specialist if:

- SF >1000 µg/L
- Cirrhosis/advanced liver disease
- Abnormal liver function tests
- Non-HFE iron overload
- Contraindications to phlebotomy
- Significant co-morbidities e.g. fatty liver disease

Treatment

HH patients with SF above the upper limit of normal should have treatment to normalise iron indices. Regular **phlebotomy** will achieve this. Phlebotomy should begin when SF is above the normal range (this is typically >200 µg/L in pre-menopausal women and >300 µg/L in men and post-menopausal women).

If there is a raised TS but normal SF, treatment is not required as it is only with raised SF that there is evidence of raised total body iron levels.

Each 500ml of blood contains approximately 250mg of iron. The aim is to keep SF between 50-100 µg/L.

Initially, the treatment can mean weekly or biweekly phlebotomy to rapidly reduce the ferritin levels. After a normal level has been achieved, maintenance may only require three or four sessions per year for the remainder of life. The frequency of phlebotomy depends on initial SF.

Phase 1. Iron Unloading Phase

- Weekly or every two weeks phlebotomy of ~500 ml whole blood until SF is <250 µg/L. Then monthly until SF has reduced to 50 - 100 µg/L.
- Ensure pre-phlebotomy haemoglobin >12.5 g/dL.
- Monitor haemoglobin every 4-6 phlebotomies. Delay for 1 week if pre-phlebotomy Hb <11 g/dL.
- Monitor SF every 4-6 phlebotomies, until approaching target values (approx. 100 µg/L), then take on each occasion.

Phase 2. Lifelong Maintenance Phase

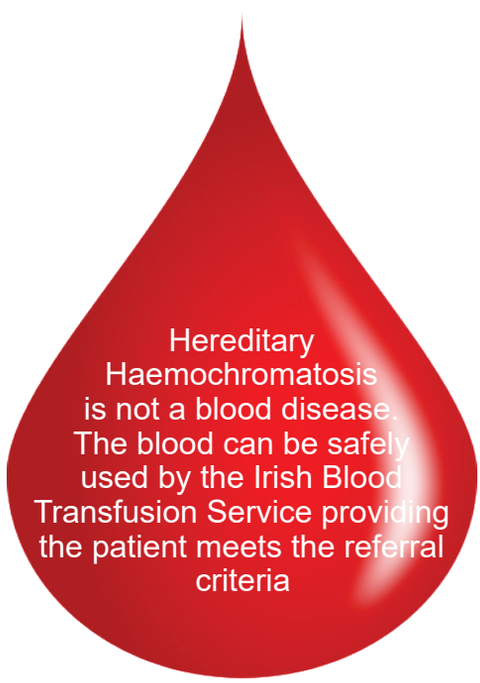
- Phlebotomy to maintain SF 50 – 100 µg/L.
- Highly variable between individuals, often in the range 2-6 phlebotomies per year.
- Check Hb and SF before every phlebotomy (do not perform if Hb <11 g/dL).
- If patient is not undergoing phlebotomy monitor SF at least once a year.

It may take many months or even years to unload excess iron. Oral supplements for vitamin B12 (5 µg daily) and folate (500 µg daily) support erythropoiesis during frequent phlebotomy.

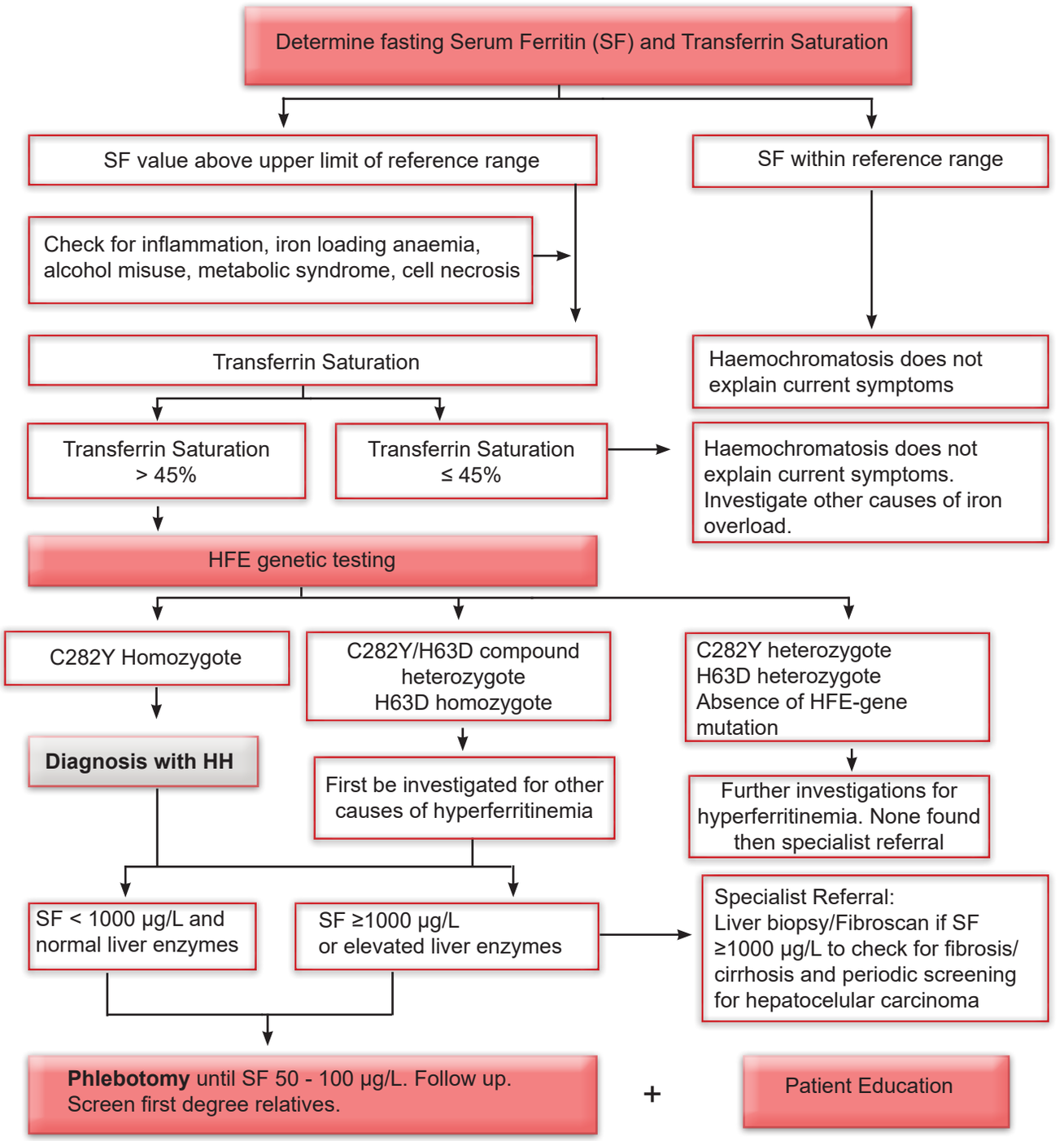
Phlebotomy services

Phlebotomy can be performed in the GP surgery. If you are unable to provide phlebotomy in your clinic, please refer the patient onto another phlebotomy clinic. Most clinics are currently based in the hospital but there are aims to move these to the community in the future.

The Irish Blood Transfusion Service (IBTS) has a therapeutic phlebotomy programme for individuals with HH and patients should be referred onto the IBTS if the referral criteria is met. This includes having SF < 600 µg/L. The service is currently available in Dublin and Cork and it is hoped to expand this service nationally. Please see https://www.giveblood.ie/ for more details.



Diagnostic flowchart for patients with suspected Hereditary Haemochromatosis



Monitoring

» Asymptomatic patients with normal SF at diagnosis should have annual TS and SF.
» If cirrhosis is present, surveillance for hepatocellular carcinoma with 6 monthly ultrasound scan and alpha feto protein levels.

Nutrition and Lifestyle

» Patients should be encouraged to eat a well-balanced diet and plenty of water.
» Patients should be advised to avoid iron supplements. There is no need for a patient undergoing phlebotomy to be prescribed a low-iron diet as the amount of iron removed by phlebotomy is far greater than that present in even a high-iron diet.
» Alcohol consumption should be kept to a minimum as moderate to heavy alcohol consumption increases the risk of cirrhosis by 10%. Abstinence is recommended in those with liver cirrhosis.
» Patients with elevated body iron should avoid raw shellfish because of the risk of Vibrio vulnificus (bacterial food poisoning)

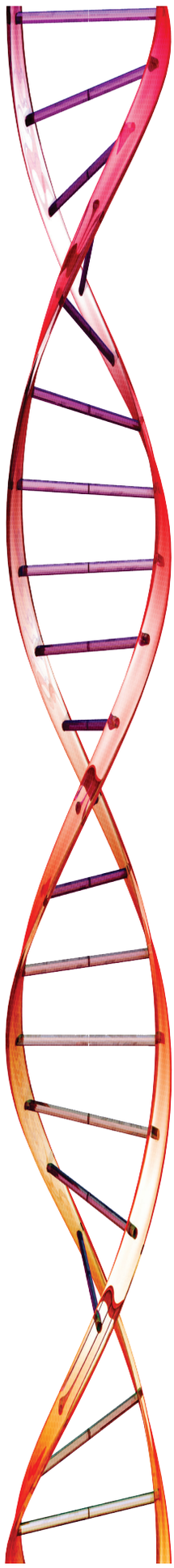
Useful Information

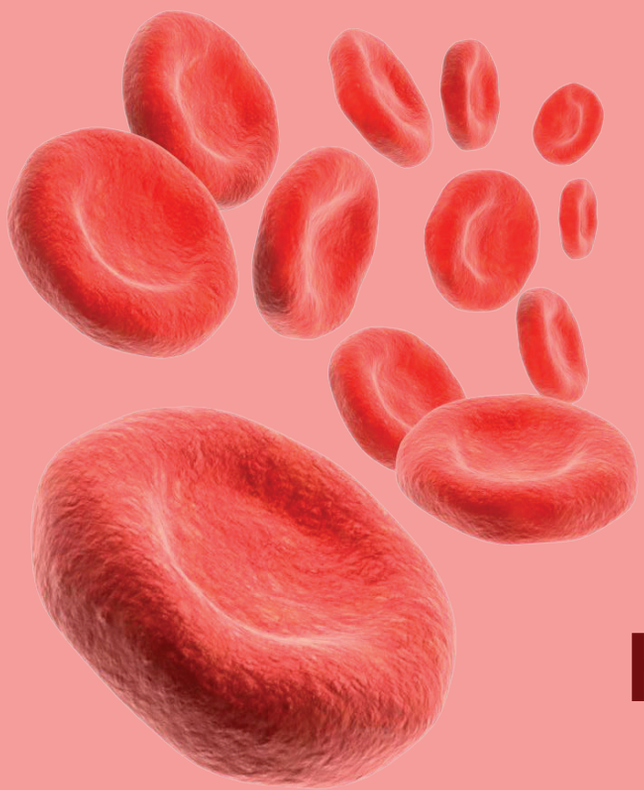
This leaflet was produced following development of the Model of Care for Hereditary Haemochromatosis and Model of Care for Therapeutic Phlebotomy

Irish Haemochromatosis Association
http://www.haemochromatosis-ir.com/

European Association for the Study of the Liver (EASL) Haemochromatosis Clinical Practice Guidelines (2010)
http://www.easl.eu/research/our-contributions/clinical-practice guidelines/detail/management-of-hfe-hemochromatosis

Hereditary Haemochromatosis – Diagnosis & Management from a GP Perspective
http://www.icgp.ie/go/library/catalogue/item/486CC79B-01FF-FE00-8856BF5F4EFEE76D





Hereditary Haemochromatosis

For Patients

What is Hereditary Haemochromatosis?

Hereditary Haemochromatosis (HH) is a common inherited disorder where the body absorbs too much iron from the diet. The iron is then deposited in, and can ultimately damage, organs such as the liver, heart and pancreas. When a person has too much iron in their body they are said to have 'iron overload'.

The treatment of HH involves the removal of some blood at regular intervals and is called therapeutic phlebotomy; it uses the same procedure as that of a normal blood donation. When this is done the body's response is to make extra blood, using up some of the stored iron.

Early diagnosis and treatment of HH prevents complications and results in a normal life expectancy.

Ireland has the highest levels of this condition in the world. Research has shown that approximately 1 in 83 people are predisposed to develop HH.

Why do our bodies need iron?

Iron, in small amounts, is essential for the production of red blood cells which carry oxygen around the body. Our bodies have no method of getting rid of excess iron, so levels are controlled by not absorbing more iron than is needed. A person with HH absorbs a great deal more iron than is necessary.

The Signs and Symptoms

No two people are alike and symptoms will vary from person to person. Generally symptoms appear when iron levels increase but some people can have high levels of iron with no symptoms. Symptoms tend to occur after the age of 40, but may be earlier or later.

The most common symptoms include:

- Fatigue, general weakness and lethargy
- Joint pain. Knuckle and first joint of the first two fingers are commonly affected
- Abdominal (tummy) pain
- Sexual dysfunction / Loss of libido
- Discoloration or bronzing of skin
- Mood swings and irritability

Symptoms of higher levels of iron in certain organs:

- Liver: Pain in liver, enlarged liver, fatigue, jaundice (yellowness of skin)
- Heart: Irregular heartbeat, shortness of breath, swollen ankles
- Pancreas: iron overload causes diabetes resulting in thirst, increased need to urinate

Most individuals who have HH will develop at least one or two of the above symptoms.

There are a number of other reasons apart from HH that can lead to increased iron levels. These include hepatitis B, hepatitis C, excessive alcohol consumption and fatty liver disease.

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Diagnosis and the Tests Involved

Your GP will perform the necessary tests for diagnosing Hereditary Haemochromatosis.

Who should be tested for HH?

- If you have the above mentioned symptoms
- If you have family members with HH. If your brother, sister, child, parent or grandparent has HH then you are at increased risk of having the same condition.
- If a relative died from liver disease (but did not have Hepatitis B/C and did not drink alcohol), liver cancer at a young age (under 60 years old), heart failure where the cause of heart failure was not known, 'bronze diabetes' (pigmented skin and diabetes).

Your GP can order blood tests to check your iron levels. If there is a reason to suspect HH you can be tested for the genes by another blood test.

Tests Involved: Iron Studies

This consists of a simple blood test to check your iron levels. It is ideally taken after an overnight fast. Both 'serum ferritin' and 'transferrin saturation' are measured.

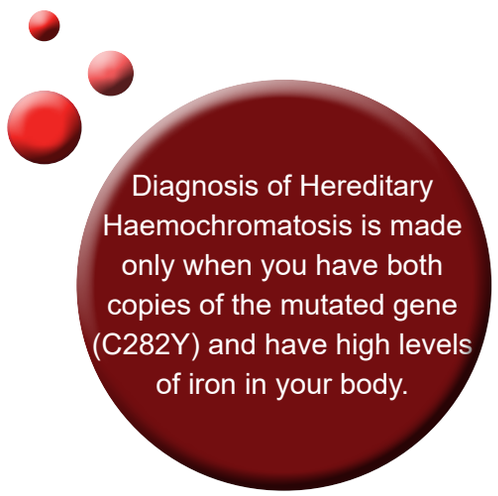
Serum Ferritin (SF)
This is an iron storage protein. A raised result may be due to iron overload but there are other causes (such as when you are ill) that can give a high result. Therefore, the result is interpreted in combination with transferrin saturation.

A SF of > 200 µg/L in women and > 300 µg/L in men suggests iron overload. If your SF is >1000 µg/L then you will be referred onto a specialist to check your liver for damage. They may perform a liver biopsy test or fibroscan.

Transferrin Saturation
This is a protein that carries iron from the gut around the body. A transferrin saturation result above >45% is strongly suggestive of HH and should prompt a genetic test.

Tests Involved: Genetic Testing

Genetic testing is only performed when you have raised Transferrin Saturation. It will test for the C282Y mutation, and in some labs, will also test for the H63D mutation. Testing of patients under the age of 18 is not recommended as it is an adult onset disease. The procedure involves a blood test.



The Genetics of HH

Each person has about 20,000 - 25,000 genes. Genes control different characteristics such as eye colour and height. HH is caused by defects (mutations) in a gene called the HFE gene. HFE has many purposes, but one important role is that it helps to control the amount of iron that is absorbed from food. There are several known mutations in the HFE gene. The C282Y mutation is known to cause HH. It is still debated whether other HFE mutations, such as H63D, causes HH and there is still no established consensus.

Everyone inherits two copies of HFE, one from their father and one from their mother.

- When a person has one mutated copy, he or she is called a carrier or heterozygote
- When a person has two of the same mutated copies, he or she is called a homozygote e.g. C282Y homozygote
- When a person has two different – but mutated – copies, he or she is called a compound heterozygote e.g. C282Y/H63D compound heterozygote.

HH is a recessive disease, this means that it only develops if you receive two mutated copies of the gene, one from your mother and one from your father.

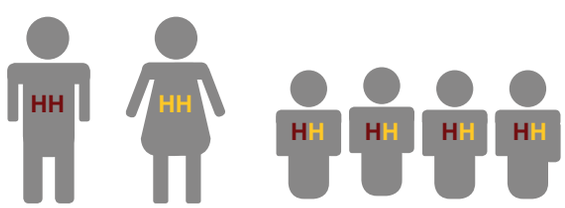
Genetics can be very difficult to understand at first. What is most important is that you know which gene combination causes the greatest known risk of loading iron. See the table below for information.

Genotype (Prevalence in Population)	Interpretation of result and risk of developing Iron Overload
Homozygous C282Y (C282Y/C282Y) (1 in 83)	Diagnosis of Hereditary Haemochromatosis is made in the presence of iron overload. Are at risk of developing HH (i.e. not everyone with this genotype will develop HH), therefore are at risk of developing significant iron overload.
Compound Heterozygous C282Y/H63D (1 in 60)	Excludes the diagnosis of the most common form of Hereditary Haemochromatosis. May be at-risk of developing mild to moderate iron overload in association with other factors (e.g. alcohol consumption) and may be considered for treatment via phlebotomy.
Heterozygous C282Y (1 in 5)	At no increased risk of developing Hereditary Haemochromatosis associated iron overload. Is a carrier of Hereditary Haemochromatosis. If iron overloaded, other causes of iron overload should be considered.
Heterozygous H63D	At no increased risk of developing HH associated iron overload. If iron overloaded, other causes of iron overload should be considered.
Homozygous H63D	At no increased risk of developing HH associated iron overload. If iron overloaded, other causes of iron overload should be considered.
Normal Genotype	At no increased risk of developing HH associated iron overload. If iron overloaded, other causes of iron overload should be considered.

Inheritance of Haemochromatosis

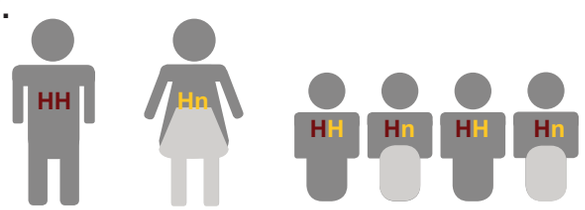
Each person has 2 copies of the HFE gene, one copy inherited from their mother and one from their father. Each copy will either be normal (n) or have the C282Y mutation (H). Therefore each person has 3 possible combinations for their HFE gene. The examples shown are averages for the whole population. However, in any particular family where both parents are carriers, it is possible for all children to be affected, all to be carriers, or all to be normal.

1.



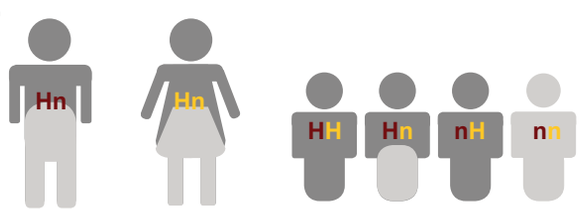
Homozygous for C282Y | Homozygous for C282Y | 100% chance Homozygous for C282Y

2.



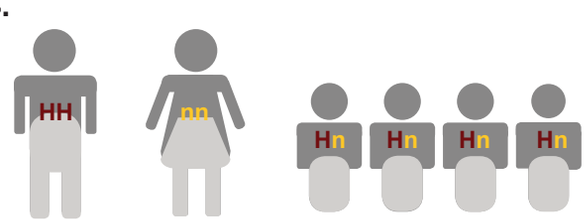
Homozygous for C282Y | Heterozygous Carrier | 50% chance - Homozygous
50% Chance - Heterozygous carrier

3.



Heterozygous Carrier | Heterozygous Carrier | 25% chance - Homozygous
50% Chance - Carrier
25% chance - Normal

4.



Homozygous for C282Y | Normal Genotype | 100% chance carriers

Management

Treatment

Treatment of HH aims to restore iron levels to a safe level. Having safe iron levels reduces the symptoms of iron overload and can help avoid complications.

Therapeutic phlebotomy, or removal of approximately 500ml of blood via a needle into the arm (same method as blood donation) is the main treatment for HH.

Phlebotomy treatment should begin when your Serum Ferritin is above the normal range (this is typically >200 µg/L in pre-menopausal women and >300 µg/L in men and post-menopausal women.)

A standard 500ml phlebotomy removes 0.25 gram of iron from the body.

Four phlebotomies remove approximately 1 gram of iron. The amount of phlebotomies you need is dependent on the amount of iron stored (ferritin) in your body.

E.g. A person with moderate iron overload may have between 4-10 grams of excess iron which will take between 16 – 40 phlebotomies to reduce to normal iron levels.

Treatment Involves Two Stages

1) Iron Unloading Stage: This involves weekly phlebotomies until your stored iron levels are in the normal range. The aim is to have your 'Serum Ferritin' around 50-100 µg/L. It may take many months or even years to unload excess iron.

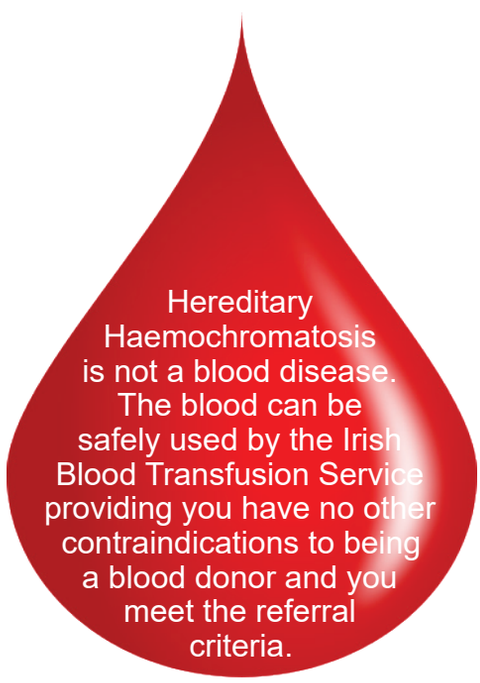
2) Life-long Maintenance Phase: You need to maintain your Serum Ferritin at 50-100 µg/L. Therefore, your iron levels will need to be monitored usually every 3 months, at least every 12 months. You may require 3-4 phlebotomies per year to ensure your iron levels are at a safe level to keep you healthy.

Treatment for HH is ongoing for life. It is important you go for regular check-ups with your GP.

Where to get Treatment

Your GP will explain where you can get therapeutic phlebotomy in your area. It can be performed by your GP or you may be referred onto another clinic to get the procedure done. Most clinics are currently based in the hospital but there are aims to move these to the community in the future.

The Irish Blood Transfusion Service (IBTS) has a therapeutic phlebotomy programme for individuals with HH and you can be referred onto the IBTS if you meet their referral criteria. This includes having your Serum Ferritin < 600 µg/L. The service is currently available in Dublin and Cork and it is hoped to expand this service nationally. Please see https://www.giveblood.ie/ for more details. It is important that when you attend the IBTS for phlebotomy you answer the questions honestly in order to ensure your safety and the safety of patients who may receive your blood.



Other Tests

If your SF is elevated, you may have other tests including fasting blood glucose, HbA1c and liver tests (ALT and AST). Other tests will be ordered according to your symptoms. These tests will be explained to you by your health care provider.

Staying Healthy During Treatment

During treatment, the number of red blood cells in your blood will also be checked. This is measured by Haemoglobin (Hb). You need to have a normal Hb before phlebotomy. Having a low Hb is called anaemia.

The frequency of your phlebotomy treatments may need to be slowed down if:

- Your Hb is too low because your body hasn't replaced your red blood cells just yet
- Your SF is too low because you are no longer overloaded
- Your blood pressure is too low.

Phlebotomy treatment will allow iron to be removed and iron stores will return to normal. However, it will not cure any clinical condition such as diabetes already present at the time treatment is started. Therefore, early diagnosis and treatment is vital.

What if I have the genetic mutations but do not have iron overload?

C282Y homozygotes and C282Y/H63D compound heterozygotes should arrange with your GP to monitor your iron levels every 12 months. You need to take no other action if they remain in the normal range.

Family Screening

If you have been diagnosed with HH it is very important that your siblings and offspring are screened for the condition. Your parents may need to be screened following an assessment by the GP on their age, sex and ferritin. If you are worried about your children, it is useful to perform genetic testing on your spouse to predict whether the children will need to be considered for genetic testing.

Diet and Lifestyle

You should eat a balanced, nutritious diet. Avoidance of dietary iron (such as red meat) has little benefit as considerably more iron can be removed in a single phlebotomy and could compromise your intake of other important nutrients. The following is advised:

» Any alcohol consumed can increase liver problems and increase iron absorption. Limit your alcohol intake to safe drinking levels. Low risk weekly alcohol guidelines for adults are:
  - » up to 11 standard drinks spread over one week for women, and
  - » up to 17 standard drinks spread over one week for men.

The standard drink in Ireland is 10 grams of pure alcohol which is equivalent to a pub measure of spirits (35.5ml), 100 ml of wine (12.5% volume) or a half pint of normal beer. Please note, it has been advised that the Irish Government lower these limits following reduction of UK limits in 2016. Please check www.drinkaware.ie for up-to-date guidelines.

If your liver is damaged you should avoid alcohol.

» Eat a well-balanced diet and drink plenty of water.

» Avoid iron supplements (including multivitamins and medication containing iron).

» There is no need for a patients undergoing phlebotomy to start a low-iron diet as the amount of iron removed by phlebotomy is far greater than that present in even a high-iron diet. If you do *not* regularly attend your appointments, restricting consumption of organ meats (such as liver) may be warranted, as these are quite high in iron

» If you are iron overloaded you should avoid raw shellfish because of the risk of vibrio vulnificus (bacterial food poisoning)

» If you are having lots of phlebotomies extra vitamin B12 and folate, either in your diet or taken as a supplement, can be very helpful. Oral supplements for vitamin B12 (5 µg daily) and folate (500 µg daily) can be taken.

» Vitamin C can increase absorption of dietary iron at meal times so should be avoided around meal times.

» HH cannot be treated by diet.

It is thought that the haemochromatosis gene originated around 40,000 years ago in Ireland in response to famine. It was spread by Vikings 'visiting' other countries.

Tips Before and After Your Phlebotomy

Phlebotomy can be hard on the body especially when you have them at high frequency. You may feel tired after treatment. It is important to look after yourself during treatment.

Before your phlebotomy, it is advised you have a balanced, nutritious meal and drink plenty of water. Drinking water helps in better flow of blood during the procedure. You should continue to drink extra fluids for 24hours after your phlebotomy.

The procedure may be uncomfortable, but it is a simple and safe procedure which is very important for your health.

The procedure itself takes about 5-10 minutes. You will need to rest immediately after treatment for at least 15 minutes. You should avoid heavy physical activity for 24 hours after the phlebotomy.

Useful Information

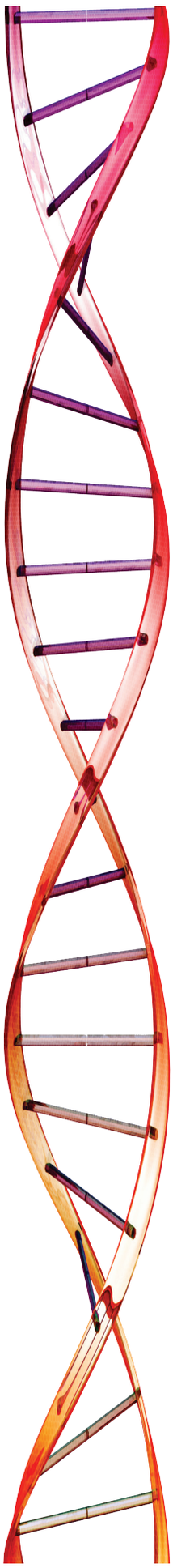
This leaflet was produced following development of the Model of Care for Hereditary Haemochromatosis and Model of Care for Therapeutic Phlebotomy. Please see the HSE A-Z webpage for more details:
https://www.hse.ie/eng/health/az/H/Haemochromatosis/

For more information about HH please visit the following:

Irish Haemochromatosis Association
http://www.haemochromatosis-ir.com/

The UK Haemochromatosis Society
http://haemochromatosis.org.uk/support/handbook/

Haemochromatosis Australia
http://haemochromatosis.org.au/



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Clinical Strategy and Programmes Division

Document Publishing Approval / Sign off Sheet

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