

Genetic

Haemochromatosis

A Guide for

Pharmacists and

Pharmacy Technicians



**The
Haemochromatosis
Society**

An Iron Overload Disorder

Support | Research | Education

haemochromatosis.org.uk

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1. Introduction

Genetic haemochromatosis (GH) is an inherited disorder. As a result of what is believed to be a combination of genetic factors a patient absorbs too much iron from his/her diet, which then accumulates within the body to toxic levels. Chronic high levels of tissue iron can lead to major complications including organ damage.

GH is potentially fatal if not identified early, i.e. before organ damage has occurred. Once identified, treatment to reduce and maintain iron levels is straightforward in most cases, though not all symptoms are reversed and organ damage may not be repaired.

This guidance will help pharmacy staff to:

- understand the causes, symptoms and dangers of GH
- discuss with patients the possibility that GH is responsible for their symptoms
- discuss with patients the implications of diagnosis
- understand the treatment for GH
- be aware of medicines that are contraindicated for patients with GH
- advise patients on lifestyle and dietary issues
- signpost patients to further sources of information and support



The most common early symptoms of GH are chronic fatigue, joint pain, skin discolouration and abdominal pain

Why is this important?

GH is thought to be underdiagnosed. The nature of the symptoms that patients present with means that often diagnosis takes place *after* organ damage has already occurred. Therefore, patient and health professional awareness of the condition is considered to be the primary method of preventing irreversible pathology. Common early symptoms (chronic fatigue, joint pain, skin discolouration, abdominal pain) may be raised initially with a pharmacist, who may also be aware of a patient's other conditions for which GH could be a contributing or causal factor (diabetes, hair loss, arthritis, etc).

Some symptoms of iron overload mirror those of iron deficiency, which can lead to anaemia misdiagnosis or incorrect self-diagnosis and the use of contraindicated iron supplements.

Early diagnosis of GH leads to simple, safe and proven treatment, which reduces suffering and the burden of long-term care. Early treatment can prevent serious, potentially life-threatening complications.

RELATED TERMS

- Types 1–4 haemochromatosis
- Hereditary haemochromatosis
- Ferroportin disease (type 4 haemochromatosis, very rare)
- Iron overload (disorder)
- Juvenile haemochromatosis (type 2 haemochromatosis, very rare)

GH is used for convenience throughout this document


2. What is haemochromatosis?

Haemochromatosis, or GH (genetic haemochromatosis), is a disorder causing the body to fail to limit iron absorption from the diet.

As a result iron can build up in the body to highly toxic levels. This is termed iron overload and is potentially very damaging or fatal.

After iron is absorbed into the body it is normally stored in the bone marrow for erythropoiesis. Any excess is stored in the liver, which can also then cope with acute high levels of iron but can only store a finite amount. When a patient exhibits chronic high levels of iron in the liver and the bloodstream they are considered to have iron overload and iron can be deposited in the heart, pancreas, and other endocrine glands. GH can also severely affect the joints, causing pain in a high proportion of patients, although the mechanism for this is not yet fully understood. Arthritis in GH patients is more prevalent in the hand, ankle and foot joints than in the general population. GH is also known to adversely affect the brain, skin and hair.

It is important to note that the genetic flaws that cause a patient to load iron are not fully understood. The vast majority of GH patients have a known mutation or mutations, but not all people with those mutations go on to load iron; indeed there is debate as to what the penetrance is. Other factors must be involved - possibly further unidentified mutations, combinations of mutations, or environmental factors - but it is not yet known what they are.



GH can be considered as having four stages ...
... identifying GH at the earliest possible stage is critical

Someone is said to be haemochromatotic if they load iron, i.e. they have moved on from simply having a known mutation. The excess builds up over a number of years and damages the organs where it is stored. It is very rare but not unknown for iron to build up to a damaging level in childhood (juvenile haemochromatosis).

Thus GH can be considered as having four stages:



1. Genetic predisposition but no symptoms or pathology
2. Iron overload but no symptoms (mutation positive, elevated transferrin saturation/serum ferritin)
3. Iron overload with early symptoms (mutation positive, elevated serum ferritin, fatigue/joint pain)
4. Iron overload with serious problems (e.g. diabetes and organ damage, especially cirrhosis)

Therefore, identifying GH at the earliest possible stage is critical.

A normal man has about 4g of iron in his body, mostly found in haemoglobin in red blood cells. Up to 1g is stored in tissue and may be used to make new haemoglobin if required. A woman has 3-4g of iron, of which the stored iron is usually less than 0.5g. In haemochromatotics it is this amount stored in the tissues, the *storage iron*, which becomes excessive. Overload is said to occur in individuals when storage iron rises to 5g; it may rise to 40g or more. These broad figures are for context and may vary considerably between individuals.

Pre-menopausal women overload to a lesser extent than men as physiological blood loss during menstruation can help reduce iron build up. Regular blood donation may slow the build-up of iron in both sexes.

Deaths due to GH occur mainly as a result of major organ damage. The most common causes are liver cancer, cirrhosis of the liver and pneumonia.

3. Epidemiology

GENETICS

The evolutionary selection of patients with mutations that cause GH make it one of the most common genetic conditions in people of Northern European descent.

GH is a recessive condition and is usually caused by mutations of the HFE gene. There are three known mutations of HFE classified by where they are located on the gene; C282Y, H63D and S65C. However, the large majority of GH sufferers will only be concerned with the C282Y (which accounts for circa 80% of identified cases) and the H63D mutation. The mutations can (but do not always) lead to the failure of the body's regulation of iron intake in the gut.

Patients with either a single copy of the C282Y or H63D mutations (termed 'carriers') typically do not overload iron and haemochromatosis in these patients is assumed to be the result of other (as yet unidentified) mutations.

Those who have two copies of either mutation (homozygotes) are at a higher risk of iron overload. Those with a copy of each of two of the mutations (compound heterozygotes) are also at risk of iron overload.

Studies are ongoing to identify other gene mutations that may help to explain haemochromatosis in patients that do not have the common mutations described above.

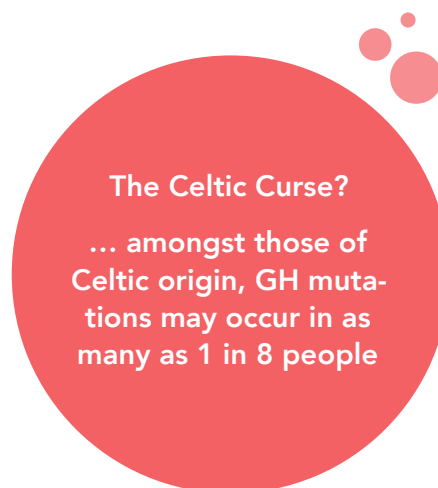
TYPES OF GH

Type 1 is by far the most common form of GH and is a result of mutations in the HFE gene

Type 2 (juvenile haemochromatosis) is a rare form of GH caused by mutations in either the HFE2 or HAMP gene

Type 3 results from mutations in the TFR2 gene

Type 4, also known as Ferroportin Disease, is a rare autosomal dominant form of haemochromatosis, a result of mutations in the SLC40A1 gene.



PREVALENCE

It is feasible that as many as 250,000 people across the UK may have a genetic disposition for haemochromatosis. However what is uncertain is the level of penetration (the percentage of those with a mutation that go on to load iron); estimates vary from less than 10% to over 30%.

In those of Celtic origin, single copy GH mutations may occur in as many as 1 in 8 people. For this reason, GH is often referred to as the 'Celtic Curse'.

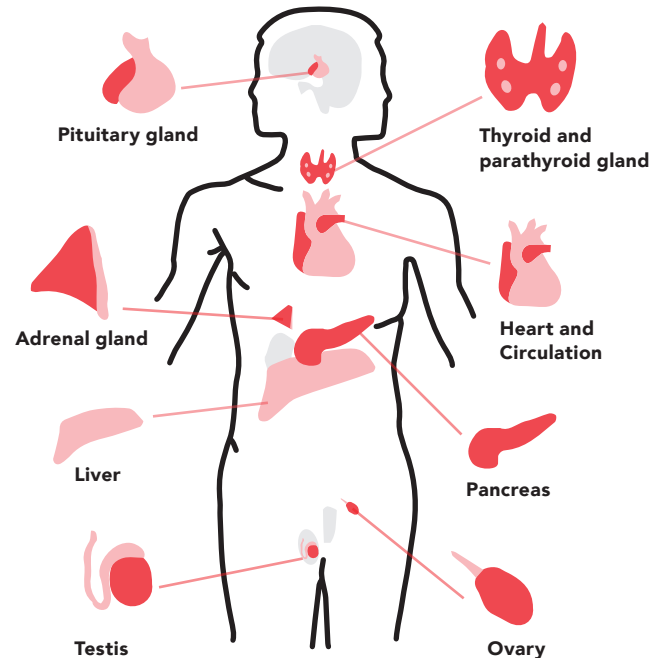
Whatever the numbers, there is no doubt that the major contributory factors preventing effective management of morbidity and mortality in GH are late diagnosis and even misdiagnosis. Other factors, including the involvement of other genes and the impact of environmental factors, are not fully understood and research is ongoing in these areas.

4. Symptoms

Being a systemic problem, iron overload causes a wide range of symptoms. Any combination of two or more of these symptoms may be indicative of GH and iron overloading.

A 2005 survey by The Haemochromatosis Society showed that members experienced various symptoms (ordered with the most commonly reported symptoms first):

- arthritis and joint pain
- chronic fatigue and lethargy
- chest pains, cardiomyopathy, shortness of breath
- mood swings, depression and anxiety
- impaired sexual function/infertility
- skin tan or grey colouration
- abdominal pain
- loss of body hair
- liver disease
- menstrual problems
- diabetes



Arthropathy in GH may affect any joint but particularly the hands and feet. The knuckle and first joint of the first two fingers are commonly affected, creating what is sometimes referred to rather inaccurately as the 'bronze fist', illustrated below.



The nature of early symptoms of iron overload are such that GH is believed to be significantly underdiagnosed in the UK

Thus if arthritis is suspected in the first two finger joints this is highly suggestive of GH and patients should be referred to their GP for serum ferritin and transferrin saturation tests.

Symptoms are often attributed to other causes, leading to delay in diagnosis. For example chronic fatigue is associated with anaemia, joint pains are attributed to ageing and lifestyle, diabetes to dietary issues, and liver problems to alcohol abuse.

Combinations of the symptoms of GH can and should however lead to early diagnosis.


5. Complications

Untreated iron overload which progresses to stage 4 (see Section 2) results in serious complications as a result of damage to major organs.

Patients may be affected by any of (or any combination of) the following complications.

- progressive arthritis to the extent that joint replacements and/or fusions are required
- worsening chronic fatigue which becomes increasingly debilitating
- cardiomyopathy and resulting heart failure
- worsening depression and other mental health issues
- cirrhosis of the liver, cancer of the liver, transplant, fatality
- type 2 *diabetes mellitus* insulin dependence

Patients diagnosed with GH should be referred by their GP to a number of specialists as a result of the symptoms and complications presented.



GH is a systemic condition. Many body functions are affected and patients might ultimately be referred to a range of specialist consultants

Haematologist

Treatment (see Section 8) is through venesection (phlebotomy). Patients are often referred to the haematology department of their local hospital even though GH is not technically a blood disorder.

Hepatologist/gastroenterologist

The root cause of iron overload is the failure of the body's processes for controlling iron absorption in the gut, however the liver is typically the tissue where iron overload damage occurs first. All patients diagnosed with GH should have liver function tests and a liver ultrasound performed. Those patients with a serum ferritin level over 1000 microgrammes per litre will have a liver biopsy performed by a hepatologist.

Geneticist/genetic counsellor

For genetic testing and family genetic counselling/testing.

Rheumatologist

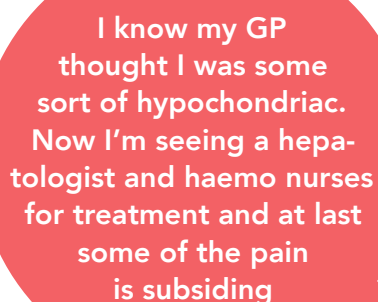
Will assess arthropathy and treat any pain. A rheumatologist may recommend surgery in more serious cases.

Endocrinologist

Pituitary and pancreatic function will be assessed by an endocrinologist.

Cardiologist

A cardiologist will investigate shortness of breath and other symptoms that may indicate cardiomyopathy.



I know my GP thought I was some sort of hypochondriac. Now I'm seeing a hepatologist and haemo nurses for treatment and at last some of the pain is subsiding

6. Factors affecting the condition

Beyond genetics, there are a number of factors that may affect the onset and progress of iron overload and the development of the various symptoms and complications.

Age

Generally (but not exclusively) symptoms begin to develop mid-life and patients in their fifth and sixth decade appear to be most affected. Build-up of iron to harmful levels can take many years. However, very rarely, young people can be affected, notably in ethnic minorities.

Gender

Due to physiological blood loss in menstruation and childbirth, iron levels build up more slowly in pre-menopausal women (in general terms) than in men and older women.


Diet

GH cannot be treated by diet, but diet can affect the rate of build-up and the ease with which iron levels are controlled once GH is identified and treatment has started. There are two forms of dietary iron:

- non-haem iron, found in cereals, fruits and vegetables, beans, pulses and nuts
- haem iron, found in meat and fish, notably red meat products and offal

Non-haem iron contributes 90% of dietary iron intake in the average UK diet but accounts for a much smaller proportion of the amount absorbed by the body. It is harder for the body to efficiently absorb non-haem iron due to its molecular make-up and because it is often found in foods that also contain components which inhibit its absorption.

The most important iron inhibitors are polyphenols and phytates. Polyphenols are found in fruits, vegetables and some beverages, notably tea, coffee and red wine. Some polyphenols have a stronger inhibitory effect than others. For example, tea polyphenols have a greater inhibitory effect on the absorption of non-haem iron from meals than those in coffee. In the UK, black tea (as opposed to green tea: it does not matter whether milk is added) is an important inhibitor because it contains high levels of polyphenols and is widely consumed.



Supplements with iron should not be recommended without considering the danger to GH patients

Phytates are storage forms of phosphates and minerals, which are found in seeds, nuts, soya, wholegrain and unrefined cereals and cereal products.

Some dietary components, notably ascorbic acid (vitamin C) and alcohol, are strong enhancers of non-haem iron absorption.

Haem iron only accounts for approximately 10% of dietary iron intake in the average UK diet. The absorption of haem iron is relatively unaffected by what is eaten at the same time. Haem iron is better absorbed than non-haem iron, and can account for half of the iron absorbed from the diet. Offal and blood products are particularly rich in haem iron, followed by red meat. White meat and fish contain less. In addition, protein contained in meat and fish enhances the absorption of non-haem iron.

Blood donation

Iron levels build up more slowly in people who give blood regularly because (as with venesection as a treatment) the body uses storage iron when manufacturing new red blood cells.

Some patients like to donate so that their blood is of use to others. However, patients with GH should not donate blood until therapeutic venesection has reduced their iron concentration to within the normal range. The blood service will accept blood donations from 'de-ironed' GH patients.

7. How GH is diagnosed

Patients with a family history of GH are far more likely to be diagnosed as being at risk of iron overload early. Those from unaffected or undiagnosed families are more likely to be diagnosed when symptoms present or become severe. This is dangerous because untreated iron overload leads to organ damage and other problems, many of which are entirely preventable. Any of the common symptoms – especially in combination – should lead a GP to arrange tests that may confirm GH.

Pharmacists and their staff have a part to play in drawing combinations of symptoms to a patient's attention and referring them to their GP for investigation.

Once suspected, diagnosis is made by a GP or consultant through the following tests. Genotyping and phenotyping both have a role to play, however the actual loading of iron as opposed to the genetic predisposition is what is really important in most cases.

Transferrin saturation (TS)

TS is the relative amount of transferrin in the body that, at the time of testing, is bound to iron. Serum iron is divided by total iron binding capacity (TIBC) to give the TS percentage. Normal average is 30% (slightly higher in men than women) and if on two separate occasions this is over 50% in men or 45% in women, GH is very likely.

A genetic test for the HFE gene mutations is positive in over 80% of those affected

Feder et al (1996)

Pharmacists have a part to play in drawing the combinations of symptoms to a patient's attention

Serum ferritin

Ferritin is an intracellular protein that stores iron and controls its release. In the serum it is an indicator of the amount of iron stored in the body. Levels significantly over 300 micrograms per litre in men and post-menopausal women, and over 200 micrograms per litre in pre-menopausal women are evidence of GH. Levels of over 10,000 micrograms per litre have been reported in extreme cases. In the early stages of iron accumulation serum ferritin may be within the normal range and so raised TS with a normal serum ferritin level does not rule out a diagnosis of GH.

Genetic testing

A genetic test for the HFE gene mutations is positive in over 80% of those affected. It will also identify family members at risk of loading iron. Prior to genetic testing and on the delivery of results patients may also be referred to a geneticist or genetic counsellor to discuss the implications for their family and the interpretation of results.

Liver biopsy and other liver tests

A small sample of the liver can be removed using a biopsy needle and examined for tissue damage such as cirrhosis. This is often recommended when the serum ferritin reading is over 1,000 micrograms per litre, or there is evidence of abnormal liver function, or the HFE gene test is negative. A form of magnetic resonance imaging (MRI) scan called FerriScan is coming into use as an alternative to liver biopsy but is only available at a few hospitals in the UK. Liver transient elastography (Fibroscan) measures liver 'stiffness'; it is a useful aid in the diagnosis of fibrosis and cirrhosis and is more widely available. This test is being increasingly used to detect or exclude more severe forms of liver damage. Other blood tests may also be ordered by a GP or consultant to test liver function.

8. Treatment and management

VENESECTION

Simple and effective treatment for iron overload consists of regular removal of blood (venesection, phlebotomy). The procedure is the same as for blood donors; every pint of blood removed contains about a quarter of a gram of iron. After venesection, the body uses some of the excess stored iron to make new red blood cells.

Treatment is based on clinical diagnosis and biochemical results even if genetic tests are inconclusive.

Initially, venesection may be once a week, depending on the degree of iron overload. Treatment may need to be continued at this frequency for up to 2 years, occasionally even longer.

After treatment, excess iron will continue to be absorbed so the patient will need occasional venesections (maintenance therapy). Typically this means every 3 to 4 months for the rest of his or her life. Monitoring of transferrin saturation and serum ferritin is used to assess whether venesection is required more or less often. The transferrin saturation will normally be maintained below 50% and the serum ferritin below 50 micrograms per litre.

The graph shows how blood iron levels change during treatment. Serum ferritin decreases steadily, but transferrin saturation remains high until iron deficiency occurs, then falls sharply.

Haemoglobin is also monitored during the venesection programme to avoid iron levels falling too rapidly. Therapy may be paused if this is the case.

Patients should be encouraged to keep a record of their own various test results and The Haemochromatosis Society provides members with record cards for this purpose. These are also available on request.

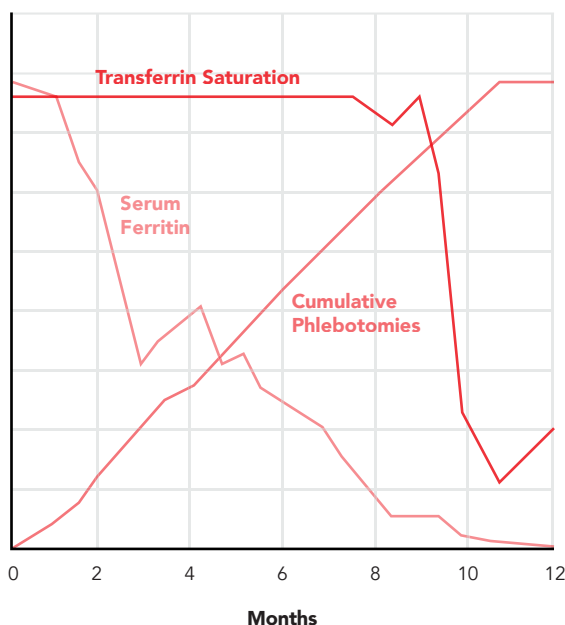
CHELATION

There are drugs that will remove iron from the body for people who have severe difficulty giving blood; these are rarely used. This is called chelation therapy and is normally used to treat iron overload caused by the multiple blood transfusions necessary for the treatment of inherited anaemias.

The most common chelating drug, desferrioxamine, is less effective than venesection and must be administered by continuous infusion, which is not pleasant for the patient. Although oral iron chelators are being developed, venesection remains more effective and is the treatment of choice for GH.

RELIEF OF SYMPTOMS

Some symptoms are relieved in some patients as iron levels are reduced in the body. For example about half of patients report an improvement in chronic fatigue symptoms and about 1 in 6 patients report reduced joint pain. However reports of improvements are by no means consistent. Severe organ and joint damage will remain if treatment is initiated too late.



9. Pharmacist advice to patients

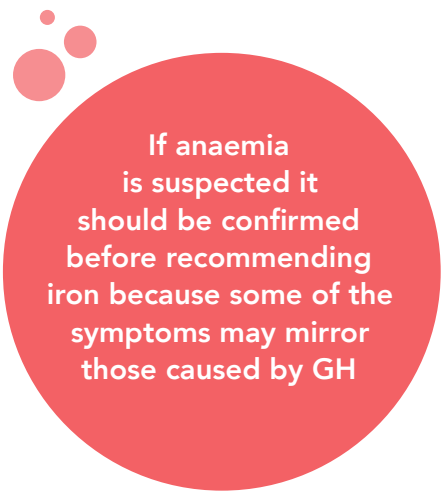
IF EXPERIENCING THE SYMPTOMS (SEE SECTION 4)

If a patient is reporting the symptoms described in section 4 for any more than a short time, they should be advised to make an appointment with their GP and request tests for iron overload (TS and SF tests). This is particularly important if:

- **joint pain in hands and feet is reported and/or;**
- **more than one of the symptoms is present and/or;**
- **there is family history of diagnosed GH or of similar symptoms**

Early diagnosis prevents severe organ damage and saves lives. Whilst it is important to counsel patients sympathetically, it is also crucial that patients with these symptoms are warned of the dangers of iron overload and made properly aware of the potential risks.

Patients should be advised to avoid the use of iron supplements as a generic remedy for chronic fatigue. Suspected anaemia should be confirmed before recommending iron because some of the symptoms may mirror those caused by GH as well as other conditions. Iron supplements and dietary supplements containing iron and vitamin C should not be recommended unless GH or other conditions have been ruled out as an underlying cause of the problems.



If anaemia is suspected it should be confirmed before recommending iron because some of the symptoms may mirror those caused by GH

IF IRON OVERLOAD IS SUSPECTED

The patient should be advised to make an appointment with their GP and request testing and referral to appropriate specialist consultants. *Patients should be strongly advised not to take dietary supplements containing iron or vitamin C until they have done this.*

Patients may find some difficulty in securing tests and referrals because the symptoms of GH are often attributed to overwork, stress, hypochondria, alcohol abuse and ageing. Levels of awareness and understanding of GH amongst GPs is very variable.

Patients should be advised to consult credible sources of information including the NHS website pages on genetic haemochromatosis, Boots WebMD and The Haemochromatosis Society (haemochromatosis.org.uk) which runs the GH Advice Line, and to then discuss this with their GP.

WHEN GH IS CONFIRMED

Patients should be advised to contact The Haemochromatosis Society, which produces *The Haemochromatosis Handbook*, a detailed resource to help patients live with GH and understand the condition and the treatment programme.

The impact of the venesection programme should not be underestimated. The process can be very tiring, painful, slow and stressful and may run for many months. Plenty of fluids and exercising before venesection can help and The Haemochromatosis Society can provide more advice and tips to help patients deal with the process.

The patient should be advised to discuss GH with family members who may be affected. GH is a recessive genetic condition and thus siblings and children are at risk. Family members should in turn be encouraged to seek testing from their respective GPs.

10. References and sources of further advice

The Haemochromatosis Society

www.haemochromatosis.org.uk

Patient organisation and source of information and support

The Haemochromatosis Handbook

www.haemochromatosis.org.uk/support/handbook/

70 page highly informative book for patients and healthcare professionals

Information for GPs and other healthcare professionals

www.haemochromatosis.org.uk/education/gps/

This is also a useful page of information for patients to pass to their GPs

Boots WebMD section on haemochromatosis

www.webmd.boots.com/a-to-z-guides/haemochromatosis

European Association for the Study of the Liver (EASL) Haemochromatosis Clinical Practice Guidelines (2010)

www.tinyurl.com/orhc5m6

Downloadable PDF of clinical information for healthcare professionals which aims to assist with the clinical decision making process for HFE haemochromatosis

NHS Choices

www.nhs.uk/Conditions/Haemochromatosis/

NHS information on haemochromatosis

Journal of Clinical Pathology (2014)

www.jcp.bmj.com/content/68/3/218

Article *Improved detection of hereditary haemochromatosis*, November 2014