

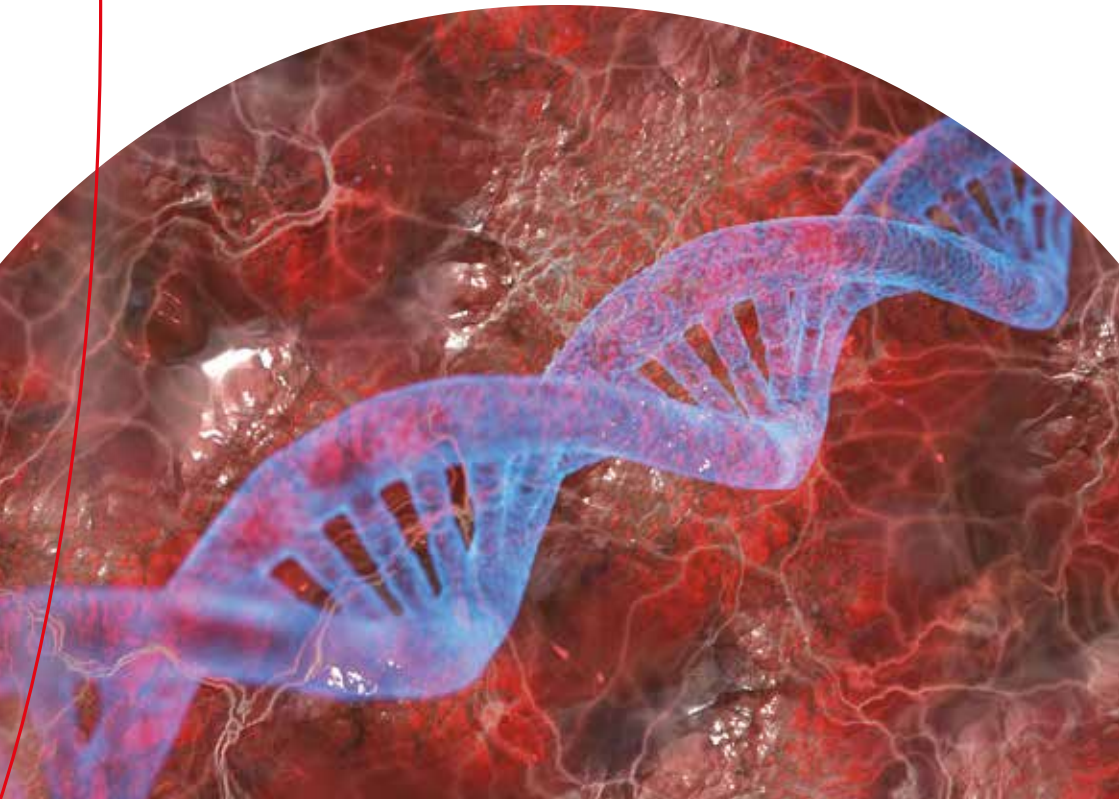
BRIEF GUIDE

General Practitioners' Quick Guide to **Genetic** **Haemochromatosis**

Haemochromatosis • UK

Helping people live with iron overload

+Fe



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Types of testing for Genetic Haemochromatosis (GH)

Serum Ferritin (SF) and **Transferrin Saturation (TS)** should be tested if a patient is presenting with symptoms of iron overload (chronic fatigue, liver disease, cardiomyopathy, diabetes, pituitary/endocrine issues).

If both SF and TS are within normal range (see table below) iron overload is extremely unlikely. If SF and TS are abnormal, genetic testing should be recommended either within primary care or after referral to secondary care. A SF of over 1000 µg/l needs urgent referral to secondary care to exclude liver damage. Referral will need to be to hepatology in this scenario; a scan of the liver to look for iron deposits may be performed.

Normal Ranges	Male	Female
Serum Ferritin (SF)	15-300µg/l	15-200µg/l
Transferrin Saturation (TS or TSAT)	16-50%	16-45%

Genetic Testing looks for the common genetic mutations which can predispose to GH. This test can indicate the cause of iron loading and/or the likelihood of a patient iron loading in the future. Genetic testing should be offered when there is a family history of the condition or in symptomatic patients.

A patient diagnosed with GH should be offered genetic screening for other first-degree family members, as there is a 1 in 4 chance that a sibling will also have it. As GH is a recessive trait, children of a GH parent will be an obligate carrier with a small risk (5%) of having GH too. Screening frequently leads to detection of GH before organ damage has occurred.

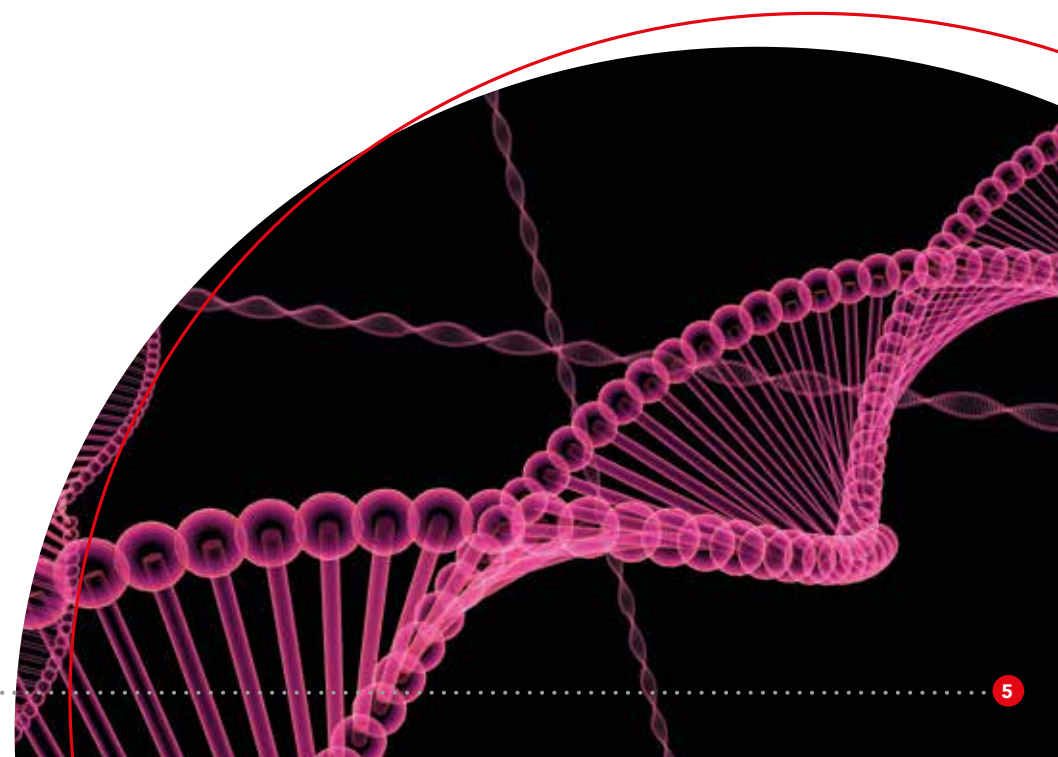
In most areas genetic testing for the common variants (C282Y and H63D) can be requested through the General Practitioner following appropriate discussions and with patient consent. For details of how this can be arranged please contact your local regional genetics service. Local regional genetic services are listed at www.bsgm.org.uk/healthcare-professionals/list-of-genetic-clinics

There are rare forms of HFE-related GH caused by other gene alterations. If GH is still clinically suspected, the patient should be referred to haematology/gastroenterology for further consideration.

Genetic counselling should be offered to families affected by haemochromatosis. Haemochromatosis UK provides free genetic counselling services for members.

For further details:

www.haemochromatosis.org.uk/genetic-counselling



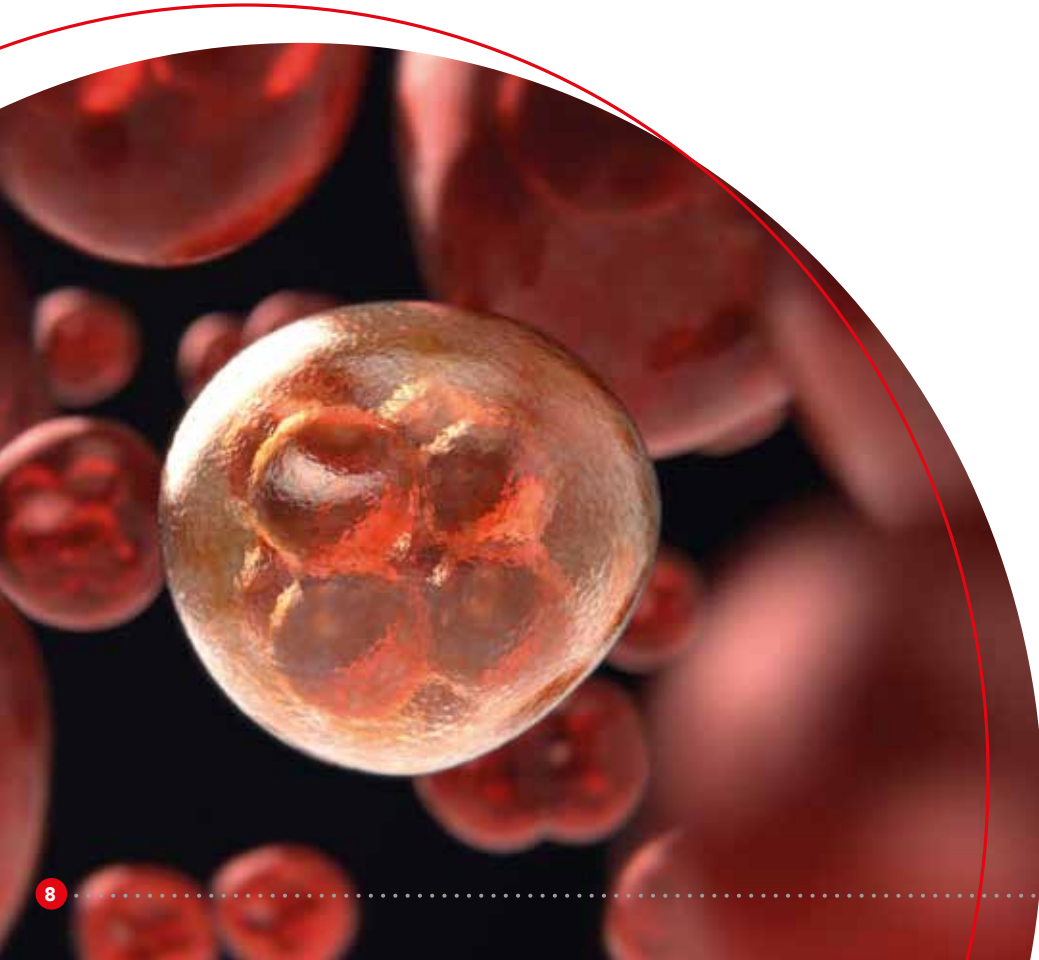
Result	Interpretation and Management
C282Y Homozygous	<p>Interpretation: Patient has 2 copies of the C282Y variant:</p> <ul style="list-style-type: none"> • Symptomatic → In men: SF>300µg/l, TS >50%, in women: >200µg/l, TS >40%. Refer to secondary care (gastroenterology/haematology) for management and treatment. • Asymptomatic → SF and TS checked annually. Patient could consider blood donation. Dietary advice to limit iron intake may offer some benefit. <p>Relatives: Biological parents and children will be obligate carriers with a low risk (5%) of being affected. Full siblings will be at a 1 in 4 risk of genetic haemochromatosis. All first-degree relatives (parents, siblings, children over the age of 16*) should be offered genetic testing via their GP.</p>
C282Y Carrier (also known as C282Y heterozygote)	<p>Interpretation: Patient carries single copy of C282Y variant. Carriers do not usually load iron.</p> <ul style="list-style-type: none"> • Symptomatic → Consider other causes of Haemochromatosis. Refer to secondary care for management/treatment. Secondary care may also consider other rarer genetic causes. • Asymptomatic → No further follow up required. <p>Relatives: At least one biological parent will be a carrier for GH. Children of patient will be at 50% risk of being a carrier. Risk of patient's parent and/or children being affected is small (approximately 3%). Therefore, testing is NOT indicated in healthy individuals.</p>
C282Y/H63D Compound Heterozygous	<p>Interpretation: Patient carries a single C282Y variant, and a single H63D variant.</p> <p>Most patients with this genotype do not load iron. However, 3 yearly checks of TS and serum ferritin are recommended. Patients should consider blood donation as a precautionary measure as mild iron loading can occur and this is usually without the typical symptoms of GH.</p> <p>Relatives: Biological parents and children will be obligate carriers for one of the variants, with a low risk (5%) of being affected. All first-degree relatives (parents, siblings, children over the age of 16*) should be offered genetic testing via their GP.</p>

H63D Homozygous	<p>Interpretation: Patient has 2 copies of the milder H63D variant. Most people with this genotype never develop symptoms or load iron.</p> <ul style="list-style-type: none"> • Symptomatic → Consider other causes of Haemochromatosis e.g. obesity and alcohol intake. Refer to secondary care for management/treatment. Secondary care may also consider other rarer genetic causes. • Asymptomatic → No further follow up or monitoring required. <p>Relatives: Both biological parents and any children will all be obligate carriers of the milder H63D variant. H63D is a milder variant and very rarely causes patients to load iron even when they have 2 copies of the variant (homozygous). Therefore, no testing is recommended for any of the patient's relatives in the absence of any symptoms.</p>
H63D Carrier	<p>Interpretation: Patient has a single copy of the H63D variant. Carriers of H63D are at a very low risk of iron loading.</p> <ul style="list-style-type: none"> • Symptomatic → Consider other causes of Haemochromatosis e.g. obesity and alcohol intake. Refer to secondary care for management/treatment. Secondary care may also consider other rarer genetic causes. • Asymptomatic → No further follow up or monitoring required. <p>Relatives: At least one biological parent will be a carrier of the milder variant H63D. Siblings and children are at 50% risk of also being a carrier of the H63D variant. As this is a mild variant, in the absence of any symptoms, no testing is recommended.</p>
Not a carrier (C282Y not present)	<p>Interpretation: Patient does not carry either of the most common variants for GH.</p> <ul style="list-style-type: none"> • Symptomatic → Consider other causes of Haemochromatosis e.g. obesity and alcohol intake. Refer to secondary care for management/treatment. Secondary care may also consider other rarer genetic causes. • Asymptomatic → No further follow up or monitoring required. <p>Relatives: Relatives do not require any genetic testing unless they themselves have an affected relative.</p>

*For children under the age of 16, partners can be tested to help inform their risk.

Ensure that affected relative's name and relationship are indicated on test referral forms.

There are other variants of genetic haemochromatosis that involve other genes, but these are exceptionally rare. Genes alone do not explain why some people go on to load iron and others do not. There are other possible factors (as yet unknown).



Variants of Genetic Haemochromatosis

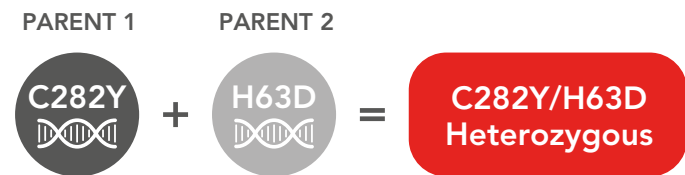
C282Y Homozygous

Most people with genetic haemochromatosis have two copies of a variant in the *HFE* (high iron) gene known as *C282Y*. They have 2 copies because they inherit one copy from each parent. This is known as *C282Y* homozygous.



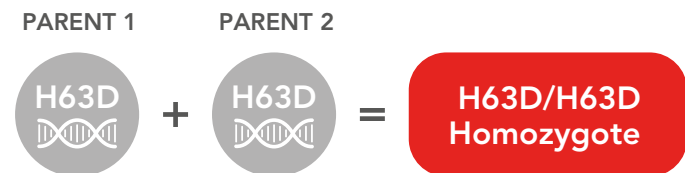
C282Y/H63D Heterozygous

A second, milder variant known as *H63D* can very occasionally predispose to haemochromatosis. If a person inherits a *C282Y* variant from one parent and a *H63D* variant from the other parent, they are known as compound heterozygous (*C282Y/H63D*). It is rare for people who are compound heterozygous to load iron in amounts that cause organ damage.



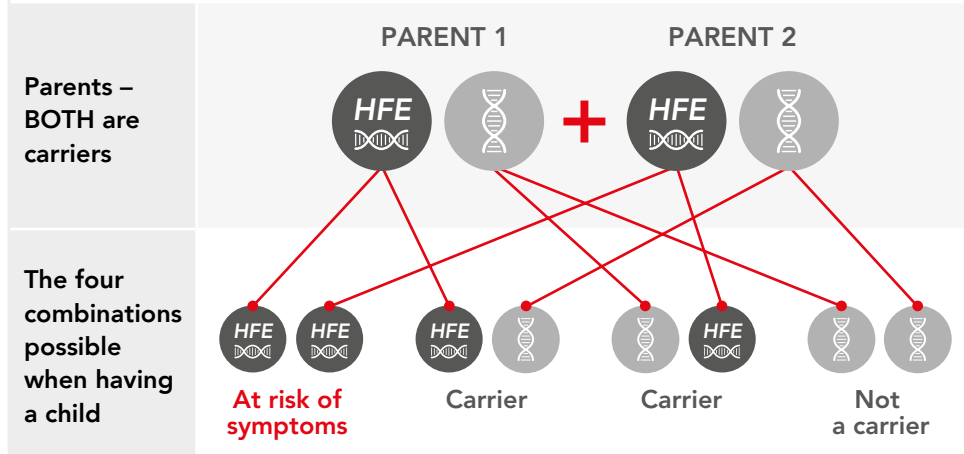
H63D/H63D Homozygote

People with two copies of *H63D* one from each parent. This is sometimes referred to as a *H63D* homozygote or *H63D/H63D*. *H63D* homozygotes are considered to have a very low risk of developing iron overload.



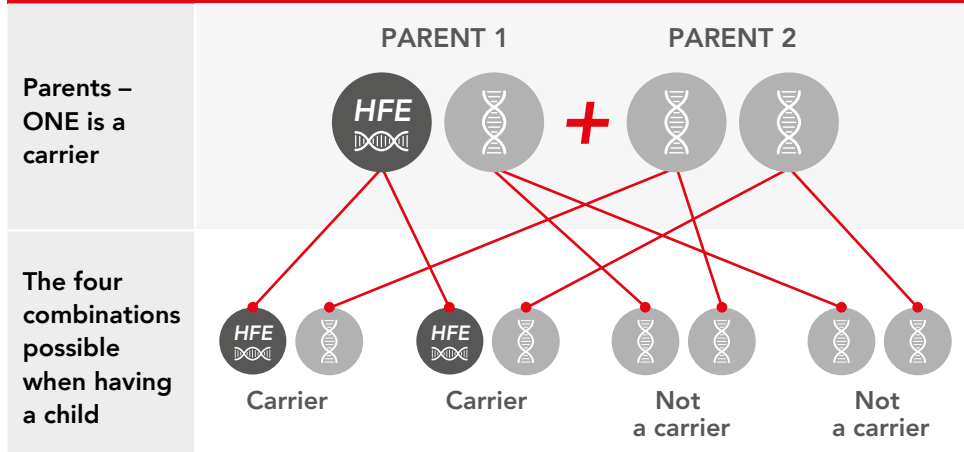
What happens when both parents are carriers for genetic haemochromatosis?

When both parents are carriers there is a 1 in 4 (or 25%) risk that any child they have together may inherit a variant from each of them. Meaning each child they have has a 1 in 4 (25%) risk of developing symptoms and iron loading as an adult. This is shown in the diagram below.



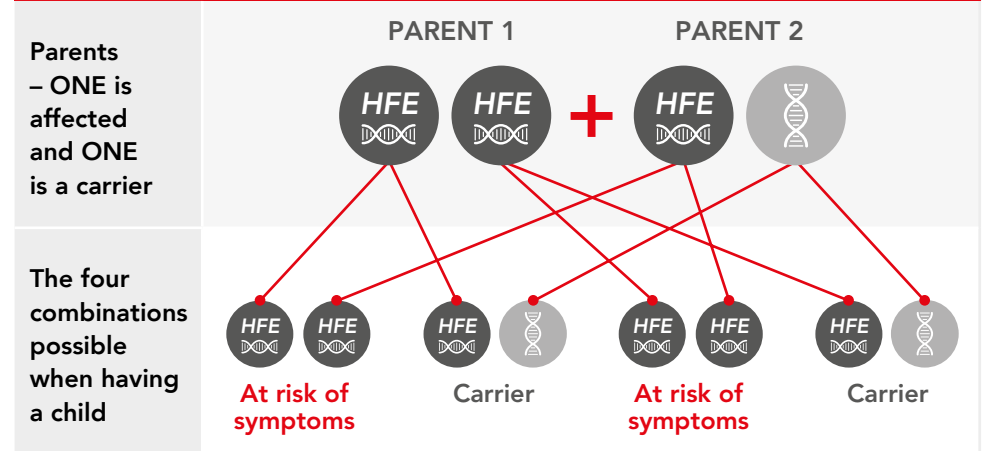
Each child has a 1 in 4 risk of developing iron overload, a 2 in 4 chance of being a carrier and a 1 in 4 chance of being unaffected entirely/not a carrier.

What happens when one parent is a carrier of genetic haemochromatosis?



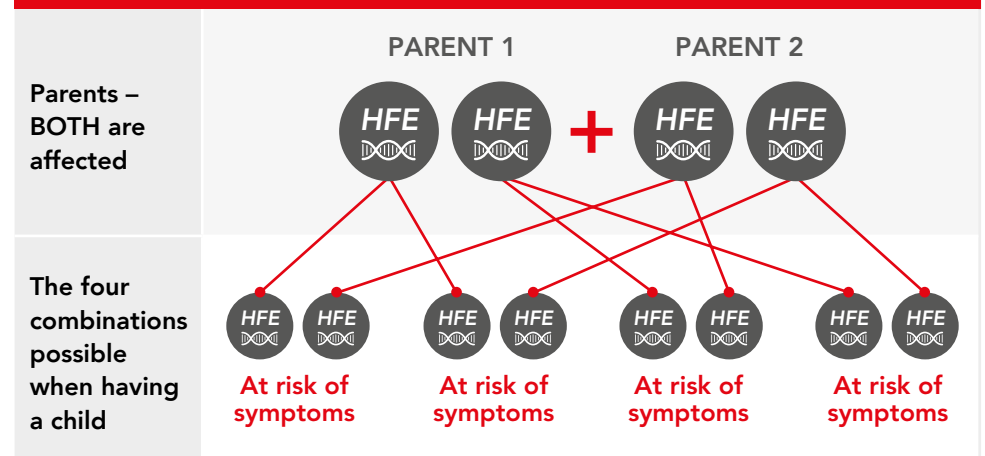
Each child has a 2 in 4 chance of being a carrier and a 2 in 4 chance of being unaffected entirely.

What happens when one parent has genetic haemochromatosis and the other is a carrier?



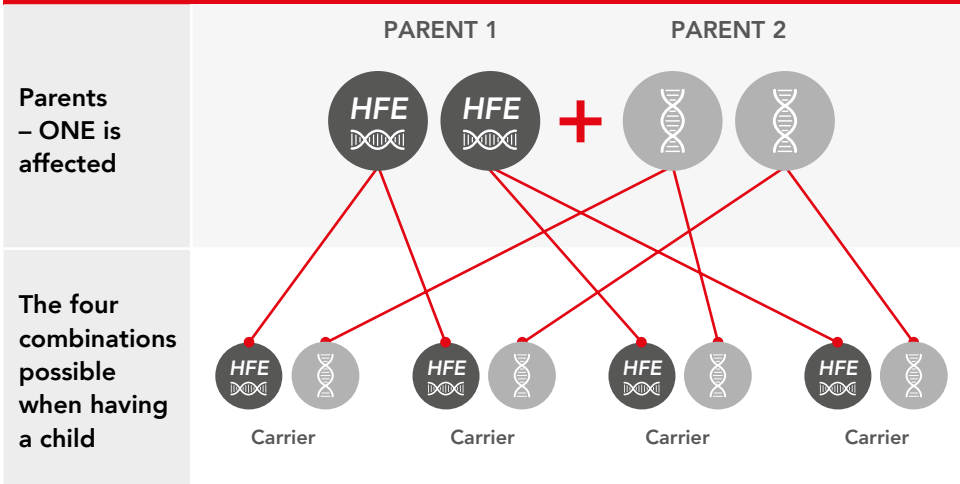
Each child has a 2 in 4 risk of developing iron overload and a 2 in 4 chance of being a carrier.

What happens when both parents have genetic haemochromatosis?



Each child is at risk of developing iron overload.

What happens when one parent has genetic haemochromatosis?



Each child will be a carrier.

Children

As GH is an adult on set condition testing is not recommended in the absence of symptoms before the age of 16. This allows for young adults to make their own informed decision about testing.

How to request a test

Regional testing labs have different test referrals systems. Some are able to accept electronic referrals, whilst others require paper referral forms (usually available at their websites). Blood sample should be 5ml EDTA. Ensure that the affected relatives name and relationship are indicated on the referral form.





This guide was written by Helen Bethell
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Become a Friend Against Iron Overload here:
www.haemochromatosis.org.uk/friends-against-iron-overload

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Contact us

We work to support anyone affected
by genetic haemochromatosis.

Join us – together we're stronger

Become a member – signup on our website.

Haemochromatosis UK Advice & Help Line

Telephone (12-3pm weekdays): **03030 401 102**

Email (24/7): **helpline@huk.org.uk**

Website: **www.haemochromatosis.org.uk**