Haemochromatosis
International

HAEMOCHROMATOSIS

Our answers to your questions

On the photograph: **siblings with haemochromatosis**

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Haemochromatosis International

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On the photograph: **siblings with haemochromatosis**

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Haemochromatosis
Some fast facts

Haemochromatosis is one of the most common genetic disorders in people of European origin, with a risk of approximately 1 in every 200-500 persons.

A person with haemochromatosis, if untreated, absorbs too much iron from their food. This excessive iron may accumulate in various parts of the body and cause damage in adults.

Symptoms such as fatigue, abdominal pain and joint aches, may occur around the age of 40. But early iron overload might have no symptoms at all, even if organ damage is already occurring.

Organs that may be damaged by iron overload include the liver, heart, pancreas, joints and pituitary/sex organs.

Iron overload can be detected by simple blood tests.

The genetic condition of haemochromatosis is also detected by a blood test.

Haemochromatosis is easily treated. Excess iron is removed from the body by taking blood in the same way as donating blood at a blood bank.

Haemochromatosis cannot be treated by diet alone.

Early diagnosis and treatment prevent complications and results in normal health and life expectancy.

What it is and how to suspect of haemochromatosis

What is haemochromatosis?

Haemochromatosis is an inherited genetic disorder. It is characterized by the accumulation of iron in the liver (iron overload) and high levels of “transferrin saturation”, a measure of iron levels in the blood.
By far, the most common cause of haemochromatosis is a genetic variant in a single gene. The variant is called C282Y and the gene is called HFE. Haemochromatosis occurs only if the C282Y variant is present on both copies of the HFE gene (one inherited from each parent). In people with a high transferrin saturation and evidence of liver iron overload, a diagnosis of HFE-related haemochromatosis can be easily confirmed by a genetic test to detect the C282Y variant.

What does “Transferrin Saturation” mean?

In the bloodstream, iron is transported by a molecule called “transferrin”, which acts like a container ship, transporting iron to where it is needed. At any one time, the amount of available transferrin that is carrying iron is referred to as the “transferrin saturation”. Normally, transferrin is only filled (or “saturated”) to about one-third of its capacity – in other words, the normal transferrin saturation is around 30%. In haemochromatosis, the amount of iron absorbed from the diet into the bloodstream is increased; this extra iron is then carried by transferrin, thereby increasing the transferrin saturation, sometimes reaching values over 100%.

My transferrin saturation is 80%: does it mean that my body is almost full of iron?

No – it simply means that the system that transports iron around your body is at 80% of its capacity. It takes years of very high transferrin saturation for body iron overload to occur, and even longer before excess iron becomes damaging to the organs and causes disease.
So, you can have a high transferrin saturation for a very long time without the organs (the liver, the pancreas, the heart) becoming overloaded with iron. The transferrin saturation tells us only that too much iron is being absorbed. To understand whether excessive iron has been deposited in the organs, you need to complement measurements of transferrin saturation with measurements of serum ferritin, which reflect the amount of excess iron in the organs. When coupled with transferrin saturation, ferritin can be very useful in providing information on body iron loading in haemochromatosis, as long as there are no other confounding conditions that may increase ferritin. For example, if transferrin saturation is 80% and ferritin 50 µg/L, there is no body iron overload, but if ferritin is >1000 µg/L, there may be significant body iron overload.

I have increased ferritin levels: does it mean that I have haemochromatosis?

Not necessarily – high levels of serum ferritin are extremely common in the population, and in most cases are **not** due to iron overload. The most common cause of high serum ferritin is “metabolic syndrome”, which is characterized by increased weight (especially abdominal circumference), high blood pressure, high blood sugar levels, high blood lipid levels (cholesterol, triglycerides), and sometimes a personal (or family) medical history of cardiac or vascular problems.
In this setting transferrin saturation is typically not increased. Other common causes of increased ferritin are inflammation and alcohol abuse. In such situations ferritin levels will decrease when inflammation subsides, or alcohol abstinence is achieved. In conclusion, iron overload caused by haemochromatosis is suspected when serum ferritin is high and *transferrin saturation is also high*.

The Genetics of haemochromatosis

I have haemochromatosis: did I inherit this disorder from my parents?

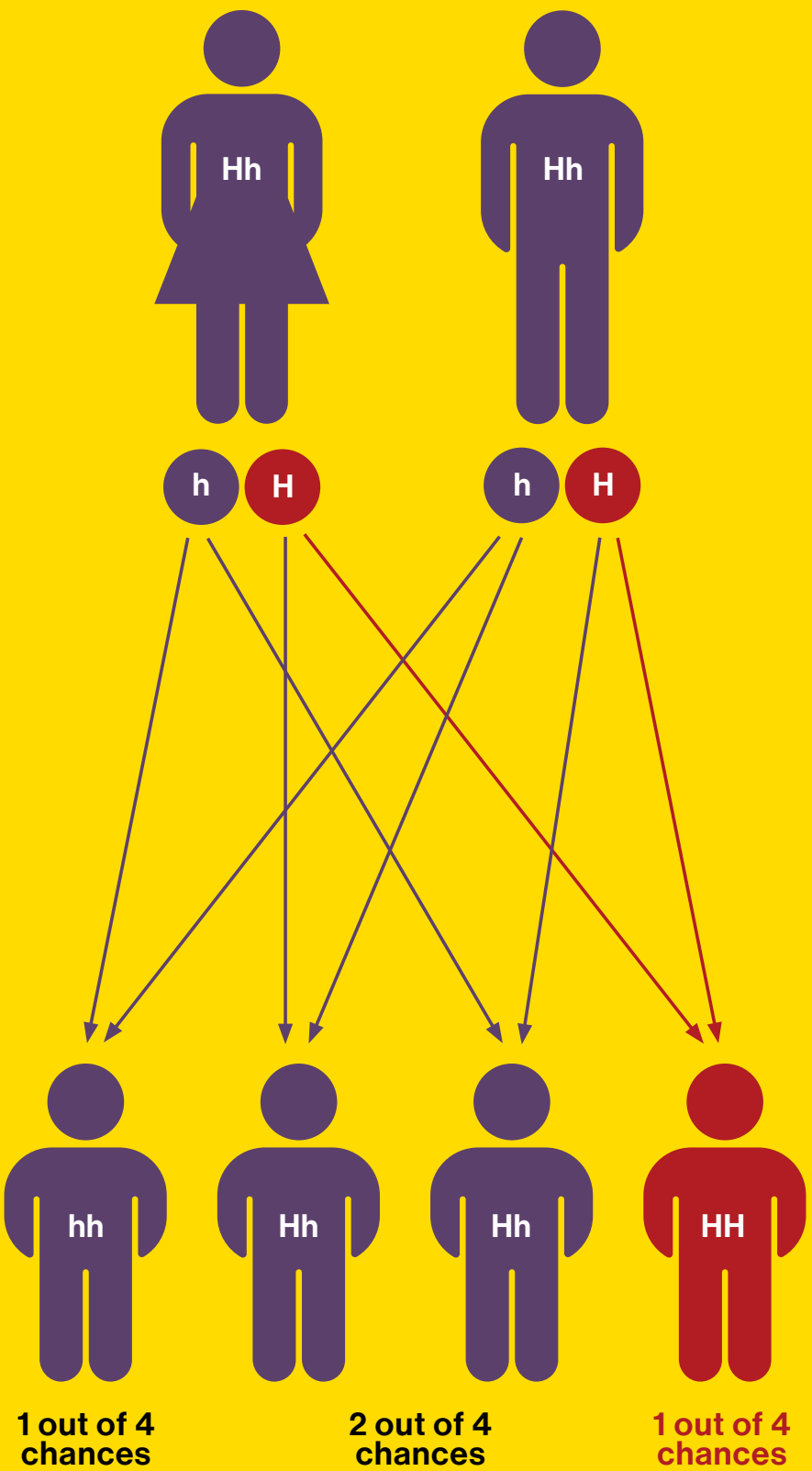
Yes – as a genetic disease, haemochromatosis is inherited from your parents. Our genes are arranged on chromosomes, and we inherit one chromosome from each parent. As a result, we have two copies of each gene (one from each parent). To have *HFE*-related haemochromatosis, a person must have the *C282Y* variant in both copies of the *HFE* gene, meaning that this variant has been inherited from both parents. This type of genetic condition, where you need two copies of the variant gene to develop the disorder, is called "autosomal recessive".

People who have the *C282Y* variant in both *HFE* genes are said to be "homozygous" for the variant. In contrast, people with the *C282Y* variant in just one of their *HFE* genes are said to be "heterozygous", or carriers. Your parents could be either homozygous for the *C282Y* variant or, more commonly, heterozygous. In the latter case they do not have haemochromatosis.

How does having two copies of the *C282Y* variant influence the development of iron overload?

The liver produces a hormone, called hepcidin, that responds to the body's iron needs by controlling the amount of iron absorbed from the diet and released into the bloodstream. For example, if the body needs more iron, hepcidin levels are reduced and more iron is absorbed from the diet. However, if the body has too much iron, hepcidin levels increase and limit the amount of iron absorbed from the diet. The *HFE* gene plays an

important role in how hepcidin responds to the body's iron needs. When body iron levels are high, HFE acts as an iron sensor and signals to the liver to produce more hepcidin, reducing iron absorption. However, the *C282Y* variant prevents HFE the protein from functioning and it loses its capacity to influence hepcidin production. This is not a problem for people with only one copy of the *C282Y* variant, as the second normal copy of the *HFE* gene can compensate for this dysfunction. But, when both copies of the *HFE* gene have the *C282Y* variant, the HFE iron sensing mechanism fails and the body continues to absorb too much iron from the diet. Over time, this leads to accumulation of iron in the liver and other parts of the body.



Is haemochromatosis always *HFE*-related?

No. In very rare cases, haemochromatosis may be caused by dysfunction of other genes, such as hemojuvelin, transferrin receptor 2 or hepcidin, which also affect hepcidin production or function. These rare forms of haemochromatosis are referred to as non-*HFE*-related haemochromatosis. They also follow an autosomal recessive pattern of inheritance, and are usually more severe with symptoms appearing early in life. In particular, the hemojuvelin and hepcidin related cases are also referred as “juvenile haemochromatosis”.

What if I have the *C282Y/C282Y* genotype but do not have iron overload?

Many people with the *C282Y* variant in both copies of the *HFE* gene (i.e. *C282Y/C282Y* genotype) do not develop iron overload. It is still not well understood why some people with this genotype develop serious iron overload and disease while others do not. Nonetheless, as the *C282Y/C282Y* genotype increases the risk of iron overload, it is important for your doctor to be aware of the situation and monitor your iron levels. If they remain within the normal range, there is no need to take any other action.

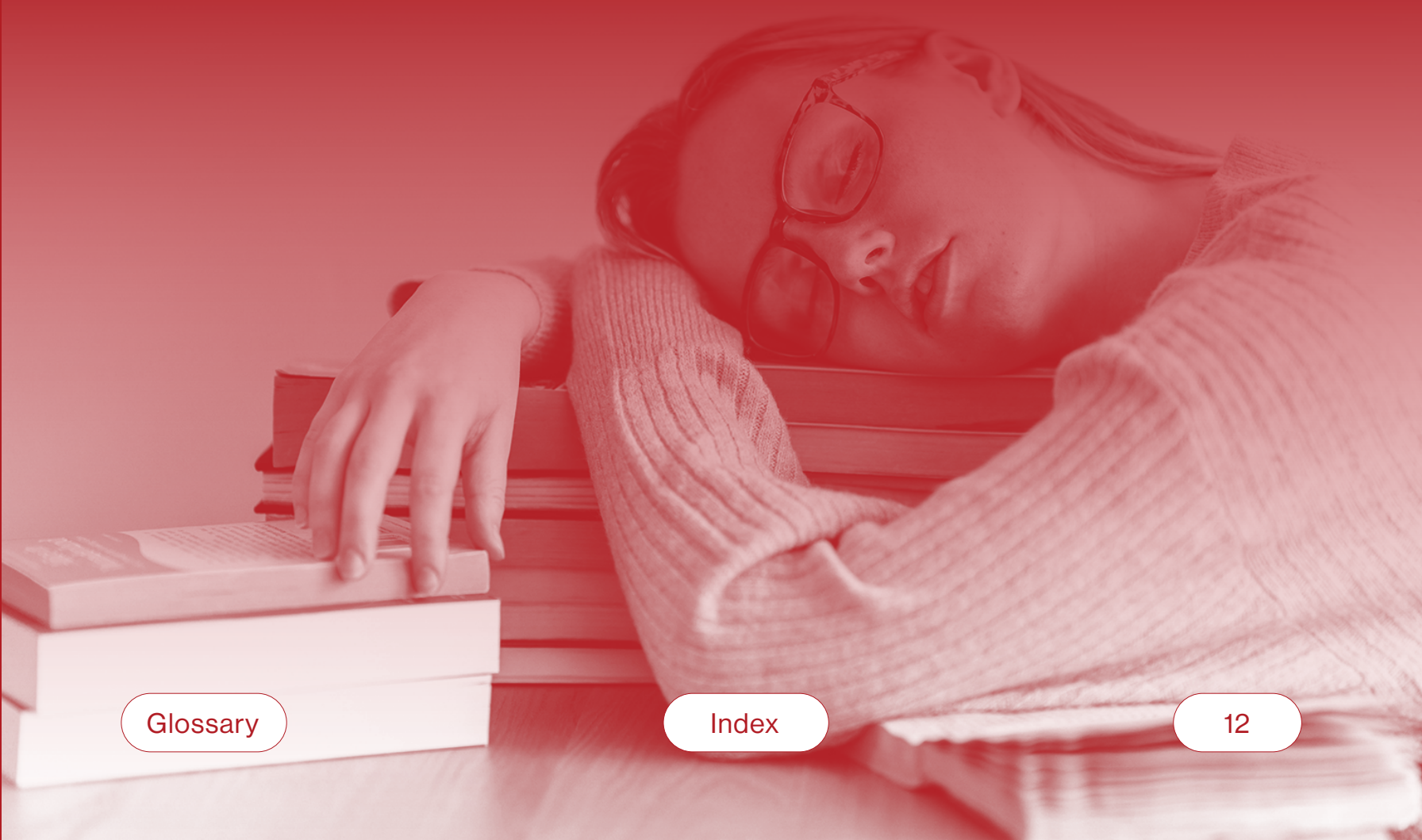
My genetic test shows *C282Y/H63D*: Do I have haemochromatosis?

No – *H63D* is another variant in the *HFE* gene very common in the general population and does not cause the same decrease in function of the gene as the *C282Y* variant does. People with a *C282Y/H63D* genotype (commonly referred to as “compound heterozygotes”) are no longer classified as having *HFE*-related haemochromatosis. While people with a *C282Y/H63D* genotype may show some increase in their measures of iron overload, particularly when combined with risk factors such as heavy alcohol consumption, chronic liver disease or metabolic syndrome, their iron levels do not become high enough to cause hemochromatosis. People with the *C282Y/H63D* genotype do not necessarily need the iron depletion treatments by phlebotomies (the standard treatment for haemochromatosis), and are generally advised to prevent liver iron accumulation by maintaining healthy lifestyle habits.

Clinical Symptoms

What symptoms may I experience with haemochromatosis?

If you have *HFE*-related haemochromatosis, you may have no symptoms at all, especially in early adulthood. Symptoms generally appear after the age of 30 and can be very diverse and non-specific; they may include unexplained chronic fatigue, sexual dysfunction (impotence), joint pain (particularly in the second and third fingers and the ankles) or sometimes an abnormally tanned complexion (although this is not an early feature). In the most advanced or severe forms of haemochromatosis other problems may develop, such as diabetes, cardiac damage (rhythm disturbances, shortness of breath during exercise), or liver problems (such as an enlarged liver and laboratory evidence of liver damage). In the rare cases of non-*HFE*-related haemochromatosis (e.g. juvenile haemochromatosis), patients may present with these more severe signs and symptoms as early as in adolescence.



I was diagnosed and treated early on, am I free of any risk of complications?

If you were diagnosed early, before the development of any irreversible damage in organs such as the liver, the pancreas or the heart, and you maintain safe levels of serum ferritin through regular blood donations or phlebotomies, you will live a healthy life free of complications from iron overload. It has even been reported that life expectancy in this setting may be longer than that of the general population. However, it is important that you continue to monitor your iron levels throughout life.The one complication that cannot be effectively treated by phlebotomy is joint disease (e.g. arthritis). If this occurs, it may need to be assessed and treated independently.

Treatment

How does the removal of blood by phlebotomies work to remove the iron stored in the body?

Our body contains about 5 liters of blood. The blood factory in the body is the bone marrow, and iron is the major nutrient to maintain this factory. Red blood cells have a lifespan of only 3 months so new blood cells are constantly produced to replace the old ones. When you remove red blood cells through phlebotomy, in the same way as making a blood donation in a blood bank, the bone marrow will increase the production of new red blood cells to replace that loss. To enable this process, iron is moved from the stores in the liver to the bone marrow, and is used there to create new red blood cells. In haemochromatosis, the red blood cells removed by phlebotomy can be easily replaced as long as there is still excessive iron in the liver. This process can be performed repeatedly, until all excess iron is depleted from the liver.

Are phlebotomies the sole treatment for haemochromatosis?

Yes. At the moment, the accepted treatment for haemochromatosis is iron depletion through phlebotomies. Following a diagnosis of haemochromatosis, the process of iron depletion involves two phases:

1. **Induction phase:** In this first phase, phlebotomies are performed intensively (usually as often as weekly) to remove excess iron from the organs as quickly as can be safely achieved. This phase may last from a few

months to a few years, depending on the amount of iron accumulated in the organs at the time of diagnosis. Some phlebotomy services offer an alternative treatment option known as “erythrocytapheresis”, where only red blood cells (not whole blood) are removed. This can reduce the number of phlebotomies required for iron depletion, and may be favored by people with particularly heavy iron loads. This treatment is not available in all hospitals.

2. **Maintenance phase:** Once iron depletion has been achieved and iron levels are within the normal range, phlebotomies are maintained in most patients on a regular but less intensive basis (2-6 phlebotomies per year) to prevent the re-accumulation of iron.

In **addition** to phlebotomy, people with haemochromatosis should aim to consume a healthy, nutritious diet, but in general can eat what they like. They should avoid consuming iron-enriched food, iron and vitamin C supplements, and moderate their consumption of red meat and alcohol. Fruit juices, especially citrus, are best consumed in moderation, and not in combination with other foods. However, these dietary recommendations only serve to reduce iron absorption from the gut and should never be considered an alternative to phlebotomy. These are guidelines only; the potential advantage to avoiding excess iron intake is that this may slightly reduce the frequency of phlebotomies needed to keep body iron stores from increasing.

Due to increased risk of infection by the harmful bacteria Vibrio vulnificus, people with haemochromatosis should avoid consuming raw or undercooked seafood (especially in the subtropical areas) and avoid contamination of open wounds with sea water.

Recent advances in knowledge about the regulation of iron absorption have led to development of new experimental drugs currently being tested in clinical trials. In the future, these drugs may provide novel alternative treatment options for haemochromatosis by decreasing dietary iron absortion. At present, these drugs have not yet been approved for use.

Where can I have my phlebotomies performed?

Your family doctor, or the specialist to whom you were referred, will recommend a treatment program for you. Phlebotomies are standardized procedures and can be performed by any doctor or nurse with experience in phlebotomy, at a hospital or medical Centre. If you are exhibiting any features of haemochromatosis-related complications, you may want to seek an assessment by a specialist physician (haematologist, hepatologist or gastroenterologist).

In many countries you can donate blood at your blood transfusion service, provided you meet the general acceptance criteria for blood donation. Your blood can be used for transfusion (as approved by the Council of Europe, the Food and Drug Administration (FDA) in the United States, or the Australian Red Cross, for example).

How do I know if my treatment is working?

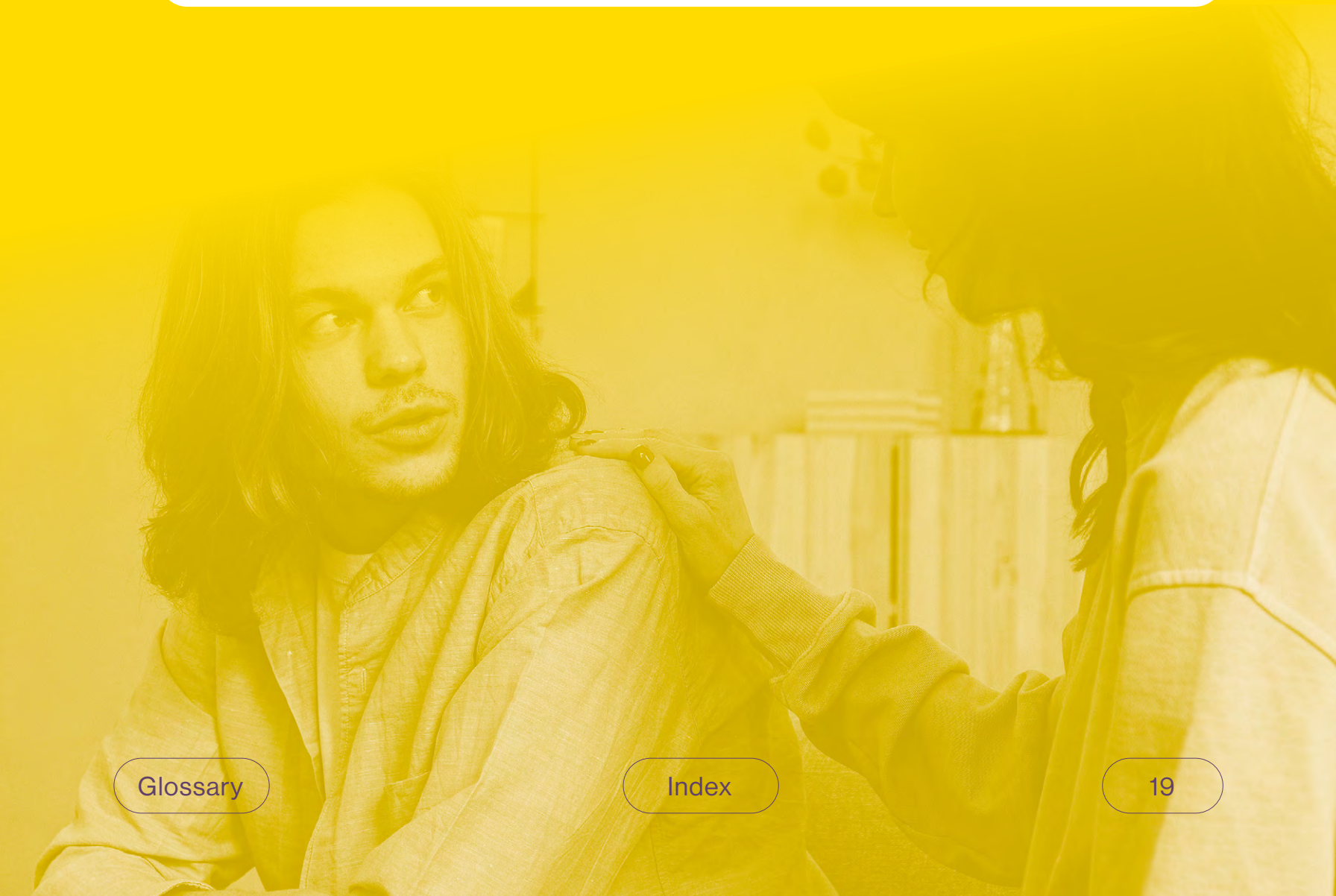
You should monitor your iron levels regularly in consultation with your doctor. Your serum ferritin level will provide the best indication of your iron stores. Once your serum ferritin has been reduced by intensive treatment to a safe level (near 50 µg/L), it is important to maintain this level (50-100 µg/L) through regular maintenance phlebotomies or blood donations. During treatment, your blood counts (such as haemoglobin level) must be maintained at your normal values, the only time point when they may decrease is at the end of intensive treatment. If for some reason your haemoglobin level drops below the reference range, your doctor might need to adjust your phlebotomy schedule to prevent anaemia.

I am now in my maintenance phase and my transferrin saturation returned to 80%: does it mean that my body is iron overloaded again?

No – Your transferrin saturation may remain high even when your serum ferritin level is low – this does not mean that you have body iron overload. As mentioned above, transferrin saturation tells us only that too much iron is being absorbed because of your genetic condition. If you try to reduce transferrin saturation through more frequent phlebotomies, you run the risk of developing anaemia. Currently, there is no strong clinical or scientific evidence to recommend target values for transferrin saturation.

Which family members do I need to inform and how do I go about it?

If you have haemochromatosis, your family members with the highest risk of having the condition are your brothers and sisters. You should inform them of your diagnosis and encourage them to seek testing. In some instances, it might be appropriate to also consider testing your parents as well, although they have a lower risk. The age and general health of your parents should be carefully considered before this is undertaken. Your children also have a lower risk but it is recommended that, when able to appropriately consent, they should also be tested. When considering the risk of very young children some doctors offer to test the patient's partner (i.e. the child's other parent). If he/she does not carry the haemochromatosis variant, their children are not at risk but will each be a carrier. If the child is still considered to be at risk, then it is recommended that they should be tested when they are able to consent to the process of testing.



Explaining some words
GLOSSARY

HAEMOCHROMATOSIS

comes from the Greek terms *haemo* (blood) and *chroma* (color); refers to the color changes associated with iron accumulation in the body

CHROMOSOME

Threadlike structure, within the nucleus of cells, carrying genetic information

GENE

Unit of hereditary information, occupying a fixed position on a chromosome

***HFE* GENE**

Gene encoding the HFE protein which plays a crucial role in iron metabolism

GENOTYPE

Genetic makeup of an organism (its composition in DNA)

PHENOTYPE

Observable expression of a genotype – essentially the “disease” or condition caused by a genetic variant

GENE VARIANT

A permanent change in the DNA sequence that makes up a gene. This type of genetic change used to be known as a gene mutation, but because changes in DNA do not always cause disease, the term gene variant is more accurate.

HETEROZYGOUS

The individual carries a variant of the gene in **one** chromosome

HOMOZYGOUS

The individual carries a variant of the gene in **both** chromosomes

COMPOUND HETEROZYGOUS

The individual carries a different variant of the gene in each chromosome

TRANSFERRIN

Protein carrying iron in the plasma

FERRITIN

Protein which stores iron within cells but is also present in the plasma

HEPCIDIN

Protein regulating iron balance of the body

PHLEBOTOMY

The therapeutic removal of blood including donation (previously known as “bloodletting”)

Help & support

Where can I get further help and support?

In most countries where the prevalence of haemochromatosis is high, patients may join associations that are part of larger federations promoting awareness and help.

You can get more information through the official sites of those Federations, such as:

HI*

*Haemochromatosis International

EFAPH*

*European Federation of the Associations of Patients with Haemochromatosis

HI and **EFAPH** share a common Joint Scientific Committee (JSC) for scientific advice.

You may also get information in the websites of your national associations, as listed at:

Member organisations HI

Member organisations EFAPH

Patients' representatives of HI and EFAPH participated as Members of a Nomenclature Committee of the International Society for the Study of Iron in Biology and Medicine (BIOIRON Society) that published the updated recommendations for the classification of

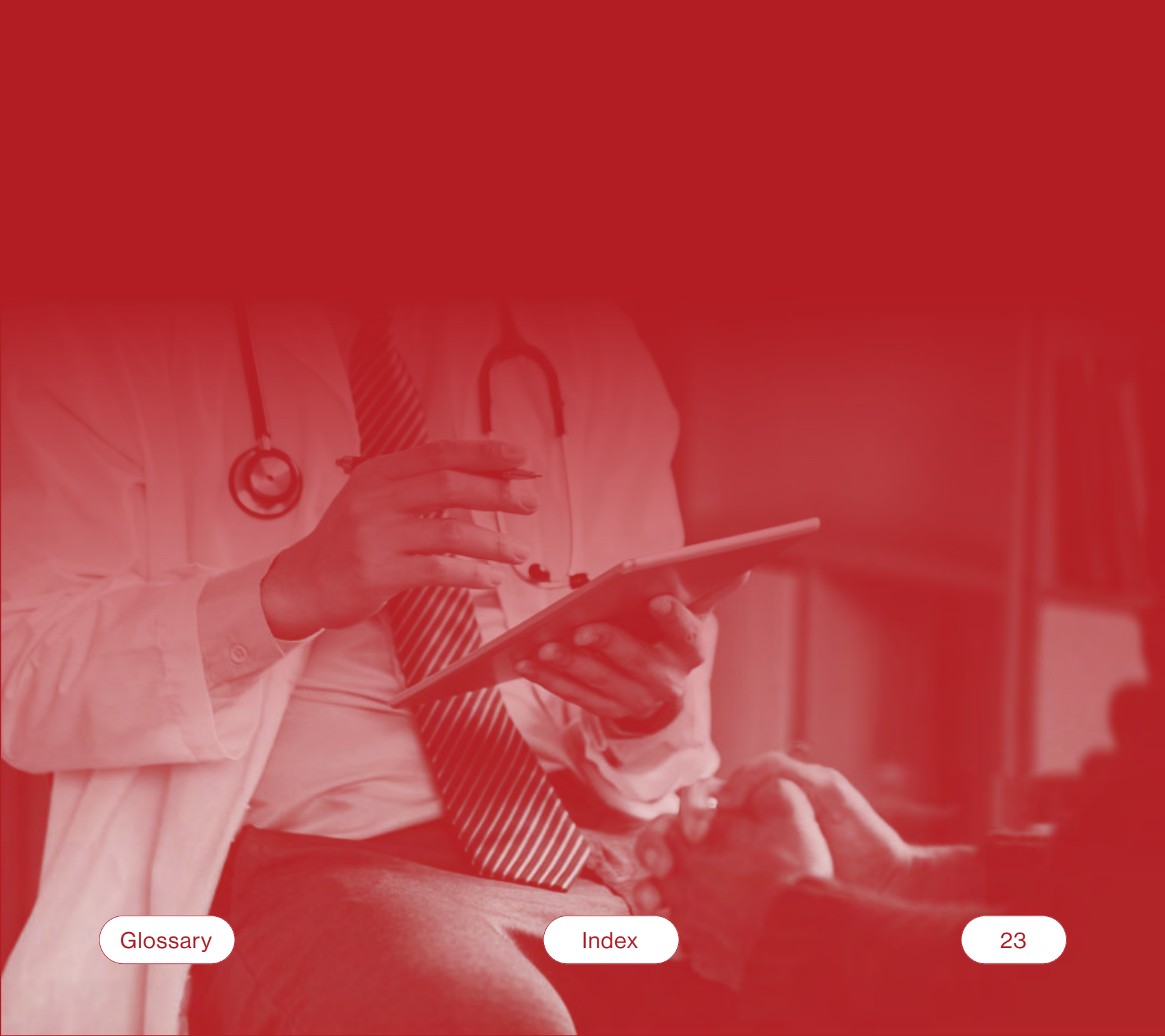
haemochromatosis which were followed in the present informative booklet.

You may find more detailed information regarding classification, recommendations and clinical guidelines at:

Girelli D, Busti F, Brissot P, Cabantchik I, Muckenthaler MU, Porto G. Haemochromatosis classification: update and recommendations by the BIOIRON Society. Blood. 2022 May 19;139(20):3018-3029.

Crawford DHG, Ramm GA, Bridle KR, Nicoll AJ, Delatycki MB, Olynyk JK. Clinical practice guidelines on haemochromatosis: Asian Pacific Association for the Study of the Liver. Hepatol Int. 2023 Jun;17(3):522-541.

EASL Clinical Practice Guidelines on haemochromatosis. J Hepatol. 2022 Aug;77(2):479-502.



Contact us

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