Identifying and managing
hereditary haemochromatosis
in adults

Hereditary haemochromatosis is the most common genetic disease in European populations. It is an autosomal recessive disorder which leads to elevated iron absorption. This in turn can lead to iron deposition in tissue which adversely influences organ function, leading to a range of complications, such as arthralgia, diabetes, heart disease, liver cirrhosis and hepatocellular carcinoma. Patients who have biochemical evidence of abnormal iron metabolism, measured by ferritin levels and transferrin saturation, require genetic testing after excluding non-specific causes of ferritin elevation. Treatment of haemochromatosis aims to reduce body iron stores by regular venesection until target ferritin levels are reached. Venesection reduces the risk of some complications, but not others, and continued monitoring of iron levels and possible clinical consequences is necessary.

Haemochromatosis is usually a hereditary condition, characterised by increased iron absorption leading to iron deposition in tissues and ultimately organ damage. Iron is an essential mineral in the diet. It is a key constituent of haemoglobin and helps regulate a number of biological processes involved in the immune response, oxygen transport and the function of various enzymes in the body, including the hepatic cytochrome enzymes. The average person has around three to four grams of iron in their body.[1] As there is no control mechanism for iron excretion in humans, iron stores in the body are regulated by controlling iron absorption; a key hormone involved is hepcidin, which is released by the liver and acts on duodenal cells to inhibit iron absorption.

In 1996 it was discovered that approximately 80% – 85% of cases of hereditary haemochromatosis are caused by common variants of the HFE gene.[2, 3] Although the molecular mechanism is not clear, these common variants increase the chances of low hepatic production of hepcidin, leading to increased iron absorption. People with this form of haemochromatosis are referred to as having HFE hereditary haemochromatosis (HFE-HH). However, the condition is recessive and people who inherit only one copy of identified genetic risk factors will not develop clinical disease. Iron accumulation in people with HFE-HH is usually not evident until adulthood.

The prevalence of hereditary haemochromatosis in New Zealand is unknown, but a study of over 1000 people in Christchurch (predominantly Caucasian) found that 38.4% of the population had at least one copy of a risk allele; however, only 0.28%, or one in 355, had haemochromatosis requiring treatment.[4]

Who is most at risk?

A patient's ethnicity is a key feature to consider when assessing their risk of hereditary haemochromatosis, and sex is a risk factor for developing clinical complications.

European ethnicity

Caucasian ethnicity is a risk factor for hereditary haemochromatosis, but people of other ethnicities may still develop the condition.

The highest prevalence of genetic risk alleles occurs in people of European descent, with prevalence in Asian and Pacific peoples one-third or less of that seen in Caucasians (see: "Genetic terminology and haemochromatosis", Page 18 for a description of risk alleles).[5] There is no direct data available on the prevalence of risk alleles for haemochromatosis in Māori.

Males are at greater risk of developing iron overload and clinical complications

Females show much lower rates of progression to symptomatic disease resulting from iron deposition.

There is no sex difference in the inheritance of haemochromatosis alleles, but males are more likely to develop iron overload and progress to clinical disease. This is assumed to result from females having greater iron loss than males, due to menstruation. The prevalence of iron overload-related complications (e.g. cirrhosis, hepatocellular carcinoma, biochemical evidence of liver damage, arthropathy) in people who are homozygous for C282Y is reported to be 28% in males and 1% in females (see: "Genetic terminology and haemochromatosis", Page 18 for an explanation of genetic terms).[6]

Who to test and what to look for

🔍 Early symptoms of haemochromatosis are non-specific

In the early stages of haemochromatosis, patients may experience vague, non-specific symptoms, such as lethargy or gastrointestinal symptoms. In more advanced haemochromatosis, symptoms arise as a result of iron overload causing damage to specific organs.

Patients may experience:[2, 6, 7]

- Early, non-specific symptoms
  - Lethargy, apathy, malaise
  - Weight loss
  - Gastrointestinal symptoms, abdominal pain

- Symptoms arising from clinical consequences:
  - Arthalgias (from joint effects; hand and knee joints are most commonly involved[8, 9])
  - Loss of libido, erectile dysfunction, amenorrhea (from reproductive system effects)
  - Chest pain, shortness of breath (from cardiac effects)
  - Weight loss, frequent urination and symptoms of diabetes (from effects on the pancreas); consider assessing ferritin and transferrin saturation in adult patients with a new presentation of type 1 diabetes
  - Sensitivity to cold, weight gain (from thyroid effects, e.g. hypothyroidism)

Signs to specifically look for on clinical examination include:[2, 6, 7]

- Liver tenderness, hepatomegaly and other signs of liver disease (e.g. cutaneous signs of chronic liver disease)
- Skin pigmentation or nail changes, porphyria cutanea tarda (discolouration or lesions on light-exposed skin such as the back of the hands), koilonychia (spoon-shaped nails)
- Oedema and signs of congestive heart failure
- Testicular atrophy and gynaecomastia in males
- Loss of body hair
- Early osteoarthritis

Biochemical testing of high iron stores

The key laboratory tests for the evaluation of body iron stores in patients with suspicious signs or symptoms are:

- Ferritin levels: increased hepatic iron stores causes elevated ferritin levels, but elevations may be due to other non-specific causes
- Transferrin saturation: transferrin binds iron in the circulation. Transferrin saturation is calculated by measuring serum iron levels and iron binding capacity.[10]

N.B. A fasting sample may improve the accuracy of results if there is uncertainty about an abnormal result.[2]

Haemochromatosis is likely in patients with elevated ferritin (> 300 micrograms/L in males or > 200 micrograms/L in females) or transferrin saturation (> 45%) levels which cannot be explained by other reasons. Elevated ferritin is a less specific marker for haemochromatosis as there are a number of clinical scenarios which can result in abnormal test results. Clinical guidelines differ as to whether elevations in both ferritin and transferrin saturation are necessary, or one alone is sufficient, for further follow-up for haemochromatosis.[2, 6, 11] Table 1 offers guidance on appropriate follow-up of ferritin and transferrin saturation results. Clinicians should **only request genetic testing in a patient with biochemical evidence of abnormal iron metabolism**[*].

Other possible reasons a patient may have elevated ferritin include:[6, 12]

- Acute illness or inflammation: the inflammation associated with an infection, or chronic inflammatory conditions, causes increased ferritin. Measuring CRP can help distinguish these patients. Evaluation of iron metabolism should be repeated or delayed until after the acute illness has resolved.
- Alcohol intake: alcohol increases ferritin levels. Patients should be questioned about their alcohol consumption and, if indicated, liver function tests requested.
- Other forms of liver disease: patients with non-alcohol fatty liver disease, hepatitis or alcoholic liver disease can have elevated ferritin levels.

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* Or if performed as part of family screening. However, screening of asymptomatic family members is not recommended unless performed under the advice of a clinician with relevant genetic experience or after discussion with a genetic counsellor, see: "Screening of first degree relatives", Page 19.

- Iatrogenic: people who receive blood or iron transfusions may have elevated iron levels following a transfusion

- Cancer: some tumours and tissue necrosis can lead to elevated ferritin[10]

- Excessive dietary intake of iron or vitamin C through supplementation

Although initial biochemical testing is performed to establish a diagnosis, it may also reveal information of prognostic importance about the presence of organ damage due to iron overload, e.g. ferritin levels > 1000 micrograms/L can indicate iron-overload induced cirrhosis.

Patients with biochemical results suggestive of haemochromatosis which cannot be explained by other diagnoses should undergo genetic testing, particularly if they have a family history or symptoms and signs of haemochromatosis.[2] Requests for haemochromatosis gene testing can be made according to local guidelines. Clinicians can contact Genetic Health Services New Zealand for advice, or refer patients to the service, if there are questions that are specifically related to family risk they cannot answer.

Further information and contact details for Genetic Health Services New Zealand is available on their website:

🔗 **www.genetichealthservice.org.nz**

For more about Genetic Health Services New Zealand, see:

🔗 **www.bpac.org.nz/BT/2014/November/ghsnz.aspx**

🔗 **www.bpac.org.nz/BT/2014/November/genetic-tests.aspx**

Incidental discovery of asymptomatic patients

Asymptomatic patients with haemochromatosis may be identified during investigation for other conditions. The finding of abnormally high iron levels in a patient, particularly if associated with abnormal liver function tests, should be considered as suspicious for haemochromatosis.[2] These findings should be followed up by biochemical testing for abnormal iron metabolism, particularly in patients with a first degree relative with hereditary haemochromatosis. A radiologist may also suggest that a patient be assessed for iron overload due to suspicious signs on radiological examinations for other conditions, e.g. chondrocalcinosis often occurs in patients with hereditary haemochromatosis.[9]

Table 1: When to request genetic testing in a patient with biochemical evidence of abnormal iron metabolism[2, 6, 11]

	Ferritin normal	Ferritin elevated
Transferrin saturation < 45%	Haemochromatosis highly unlikely; other reasons for any signs or symptoms should be investigated	Haemochromatosis possible; investigate other reasons for elevated ferritin and if other causes ruled out (and elevated ferritin persists), proceed to genetic testing
Transferrin saturation > 45%	Proceed to genetic testing for haemochromatosis	Proceed to genetic testing for haemochromatosis

Genetic terminology and haemochromatosis

Alleles versus mutations and genetic testing for haemochromatosis:

Mutations are changes in the genetic code which are rare in the population (with a prevalence of <1%)

Alleles are differing versions of a gene which are common in the population. For any gene there are usually at least two relatively common alleles in the population.

Alleles of the HFE gene which contribute to the development of haemochromatosis are common. For example, in a study in Christchurch, 38.4% had at least one risk allele (out of 1064 people).

Most cases of haemochromatosis are due to common risk alleles of the HFE gene and these are assessed in routine genetic testing for haemochromatosis. However, some patients may develop haemochromatosis due to other mutations in genes involved in iron metabolism. Further genetic testing would be required to identify underlying genetic causes of haemochromatosis in these patients.

Haemochromatosis allele terminology

There are two main alleles of interest for the investigation of haemochromatosis: C282Y and H63D. In laboratory test results or clinical correspondence, these alleles may be written in different ways but are all synonymous:

- C282Y allele: may also be referred to as Cys282Tyr or Cys → Tyr 282
- H63D allele: may also be referred to as His63Asp or His → Asp 63

Homozygous and heterozygous: This refers to how many copies of a mutation or allele a person has. Someone who is heterozygous has one copy, someone who is homozygous has two. Most cases of haemochromatosis are due to people being homozygous for the C282Y allele.

Recessive versus dominant: In genetic conditions which are dominant, patients only need to have one copy of an allele or mutation to develop a clinical condition. Hereditary haemochromatosis is recessive, so that a person who has one copy of a risk allele is not at risk of developing complications from iron overload; two copies are necessary.

Penetrance: This term describes how likely it is that someone with a specific genotype will develop a clinical condition. The risk alleles for hereditary haemochromatosis show low penetrance: only 10% of people homozygous for haemochromatosis risk alleles develop the clinical effects of haemochromatosis. For this reason, genetic screening of the general population is not recommended.[2]

In summary, many people in the population have at least one risk allele for haemochromatosis. However, a person would need two copies of common risk alleles to be at risk of developing haemochromatosis (or have other rare dominant mutations). Even with two copies of common risk alleles not all people will develop symptoms or biochemical evidence of abnormal iron metabolism.

Genetic testing for hereditary haemochromatosis

Standard genetic testing for haemochromatosis assesses whether a patient has common risk alleles and how many copies they have.

A diagnosis of HFE hereditary haemochromatosis can be made on the basis of biochemical signs of iron overload (increased ferritin and/or transferrin saturation) and the presence of risk alleles.

Most cases of hereditary haemochromatosis (approximately 80%) are due to a patient inheriting a C282Y allele of the HFE gene from both parents (homozygous for the C282Y HFE allele).[2] This C282Y allele is known as the major risk allele. Another risk allele is H63D; this is more prevalent in the population but less likely to cause haemochromatosis and is referred to as a minor risk allele. Approximately 5% of cases are due to inheriting one copy each of the C282Y and H63D alleles (referred to as "compound heterozygous").[3]

The most important findings from genetic testing for the diagnosis and management of patients are identifying those with:

- **Two C282Y alleles, i.e. homozygous for the major risk allele.** These patients are most likely to develop iron overload and clinical complications

- **One C282Y allele and another minor risk allele** (e.g. a C282Y/H63D genotype). People with this genotype may also develop haemochromatosis although are less likely to do so than people homozygous for two C282Y alleles. Particular attention should be paid to excluding other causes of elevated ferritin before establishing a diagnosis of haemochromatosis in these patients.

- **Variant genotype.** Biochemical evidence of iron overload or even elevated iron stores on liver biopsy but with a genotype other than those above (e.g. patients with a H63D/H63D genotype with elevated ferritin).[2, 13] These patients do not develop sufficient iron deposition to progress to clinical disease and can be reassured that they do not need treatment.[2]

Genetic testing forms part of the diagnostic process and can provide some prognostic information, however, clinical management and treatment is the same for all individuals with hereditary haemochromatosis who develop iron overload, regardless of their underlying genotype.

Screening of first degree relatives

Upon learning they have a condition with a strong genetic component, patients may enquire about genetic testing of family members or relatives. In general, the evaluation of family members should follow the same diagnostic process described here: family members with symptoms or signs that may be suggestive of haemochromatosis should have ferritin and transferrin saturation tests performed to establish whether they have biochemical evidence of abnormal iron metabolism, and if so, be followed up with genetic testing.

Hereditary haemochromatosis is an adult onset disorder, so testing children in affected families is not indicated.

Once children reach adulthood, the family diagnosis can be discussed with them and if patients without symptoms or biochemical evidence of altered iron metabolism wish to undergo genetic testing they should first be referred to a genetic counsellor; Genetic Health Services New Zealand recommends that genetic testing of asymptomatic adult family members of an affected individual should only be undertaken following the recommendation of a clinician with relevant genetic experience or after discussion with a genetic counsellor. It is important to note that people can be genetically at risk, with one of the above combinations of haemochromatosis alleles, but not progress to develop haemochromatosis. Therefore, genetic testing of asymptomatic family members may identify people who are genetically at risk but without biochemical evidence of abnormal iron metabolism or suspicious symptoms and signs. If this is the case, these family members should have serum transferrin and ferritin levels measured annually to monitor the potential development of iron overload.[6]

Non-HFE hereditary haemochromatosis and other diagnoses

Patients with unexplained elevated ferritin or transferrin saturation, or clinical signs suggestive of haemochromatosis but without identified HFE risk alleles after referral to genetic testing services should be followed up, particularly if aged 20 years and under (see "**Other forms of haemochromatosis**"). Referral to a haematologist is recommended.

Some patients, with a family history of the condition, develop haemochromatosis but without identifiable risk alleles or

mutations in the HFE gene, and are classified as having non-HFE hereditary haemochromatosis. These patients are uncommon, making up approximately 5% of all people with hereditary haemochromatosis.[2] Risk alleles or mutations in other genes involved in iron homeostasis may be the underlying cause of their condition. Standard genetic testing for haemochromatosis assesses the presence of common risk alleles and screening for other alleles or mutations would only be performed if there were indications for doing so.

Patients with unexplained biochemical evidence or signs of iron overload may require investigation for rare diagnoses: ineffective erythropoiesis, such as in β-thalassemia, can cause inappropriately high iron levels; patients may show signs such as splenomegaly or jaundice or have biochemical evidence of microcytosis and hypochromia.[1, 14]

Following diagnosis: treatment and prevention of complications

Following a diagnosis, the most important clinical steps are to investigate patients for the presence of haemochromatosis complications and initiate treatment. Patients should be assessed for the presence of complications arising from iron overload and treated, such as diabetes mellitus, joint disease, endocrine disturbances (hypothyroidism and hypogonadism), cardiac disease, porphyria cutanea tarda and osteoporosis.[6]

The key clinical intervention for treating haemochromatosis is venesection (phlebotomy) to reduce iron stores. **Clinical guidelines recommend that all patients with haemochromatosis are offered venesection to normalise ferritin levels.** Some patients with hereditary haemochromatosis may maintain mildly elevated iron stores without progressing to clinical complications, such as liver disease, arthropathy, heart problems or other conditions resulting from iron overload. For these patients venesection may represent a form of overtreatment. However, as there is no reliable method of predicting which patients will develop complications, and venesection is a low-risk procedure, clinical guidelines recommend offering venesection to all patients with elevated ferritin levels.[2] Where venesection is not initiated, patients should be monitored for worsening of biochemical measures of iron overload or the development of clinical complications, and to report if suspicious symptoms develop.[2]

Other forms of haemochromatosis

Haemochromatosis in young people
Younger patients (aged 20 years or less) with biochemical evidence of abnormal iron metabolism or suggestive signs and symptoms may have juvenile haemochromatosis. This is a rare condition caused by mutations in genes other than HFE, and results in more extreme iron overload and a worse clinical prognosis than HFE hereditary haemochromatosis in adults; they are likely to require follow-up with a haematologist.[2]

Iatrogenic haemochromatosis
In a minority of patients elevated iron can occur due to non-hereditary causes, such as excessive iron intake due to supplementation, or from receiving blood transfusions on an ongoing basis resulting in inappropriately high iron levels.

Table 2: Key practice points for venesection in hereditary haemochromatosis[2]

How often should venesection be performed?	How much blood should be removed?	Measures during treatment		Measurement targets
		Analyte	**When to measure**	**Measurement targets**
Initially every one to two weeks until ferritin normalises	500 mL (one unit) per session	Haematocrit Haemoglobin	Baseline and before each session	Within 80% of baseline values – delay venesection if values fall below 80%
		Ferritin	Baseline and check after four venesections	50 – 100 micrograms/L

Referral for ultrasound and liver biopsy

Patients with haemochromatosis and ferritin levels > 1000 micrograms/L have been found to have a prevalence of cirrhosis ranging from 20 to 45%.[2] As raised liver enzymes may also indicate cirrhosis, it is recommended that:[2]

- Patients with ferritin > 1000 micrograms/L undergo an ultrasound and liver biopsy

- Patients with ferritin < 1,000 micrograms/L and with altered liver enzymes (AST, ALT) undergo an ultrasound and liver biopsy

It has been reported that a study of 670 patients with two haemochromatosis risk alleles found that ferritin levels > 1000 micrograms/L had a 100% sensitivity and 70% specificity for identifying cirrhosis, and conversely, no patients with cirrhosis had a ferritin level < 1000 micrograms/L. See "**Monitoring clinical complications**", Page 24, for further information.

Liver biopsy is the gold standard technique for the assessment of liver complications in patients with haemochromatosis, as it allows for the histological assessment of the degree of liver damage and direct measurement of hepatic iron content.[2] Liver biopsy can be prone to sampling error, and ultrasound assessment of the liver allows a wider assessment of the distribution of cirrhotic or fibrotic liver tissue.[15]

Venesection normalises ferritin levels

Venesection to reduce iron stores may be performed under the guidance of a haematologist or a general practitioner. For patients unable to tolerate venesection or where it is contraindicated, referral to a haematologist is recommended; treatment with deferoxamine mesilate (subcutaneous infusion for iron overload) in a hospital setting may be an option.

The aim is to reduce ferritin levels to 50 – 100 micrograms/L by having patients undergo venesection every one to two weeks, removing 500 mL of blood each time, until this treatment target is reached. This amount of blood would typically contain 200 – 250 mg of iron.[2] Targeting treatment below 50 micrograms/L has been found to cause a paradoxical increase in iron absorption.[2] Table 2 shows treatment and monitoring information for patients undergoing venesection.

There is a high degree of individual variability in the rate of iron accumulation after venesection ceases, and little evidence to guide subsequent monitoring and treatment.[2, 6] Current practice is for patients to be monitored for changes in serum ferritin and transferrin saturation to guide when or whether to re-initiate venesection.

Adverse effects and patient experiences of venesection

Patients often experience adverse effects with venesection treatment and these are similar to the adverse effects of blood donation. Most commonly these include tiredness, loss of appetite and pain or discomfort at the needle site.[16] Light-headedness and fainting during or after the procedure is also possible.

In one survey of over 200 patients, 50% reported experiencing adverse effects during most or all venesection treatments. In addition, the time burden of attending regular venesection sessions was rated as influencing their work or daily routine "most of the time" or "all of the time" by 50% of patients. However, there was an overall high level of acceptance of venesection, with 87% of patients regarding treatment as worthwhile and only 16% reporting that they would opt out of venesection if another treatment was available.[16]

Patient guides and resources:

- Leukaemia and Blood Cancer New Zealand: a patient guide to haemochromatosis and venesection record book are available at: **www.leukaemia.org.nz/page/387**
- Since 2011 haemochromatosis patient support has been available from Leukaemia and Blood Cancer New Zealand, which was formerly provided by IRONZ, the New Zealand Haemochromatosis Support & Awareness Group: **www.leukaemia.org.nz**

Treatment improves some symptoms and complications, but not others

Patients undergoing venesection often experience improvement in subjective symptoms of lethargy and abdominal pain, and changes in skin pigmentation. Biochemical measures of liver function and diabetes control (if present) generally improve, and liver fibrosis has been shown to reverse in 30% of cases.[10] However, venesection does not reverse all the characteristic symptoms and sequelae of iron overload: liver cirrhosis, arthropathy, testicular atrophy or thyroid dysfunction, and the symptoms patients experience as a result of these complications, usually do not improve with treatment.[10] Consultation with, or referral to, an appropriate specialist is recommended for the management of complications due to haemochromatosis.

Studies suggest that patients with haemochromatosis who are adequately treated, and do not have liver cirrhosis or diabetes, have the same life expectancy as the general population.[6]

Dietary advice

Given that haemochromatosis involves increased iron absorption in the gut, restricting dietary iron would appear at face value to be an intuitive treatment. However, there is limited evidence to support a change in diet. Patients with haemochromatosis should avoid dietary supplements containing iron, and also avoid supplements with vitamin C.[3, 6, 10] Since people with haemochromatosis are already at risk of liver disease, it is recommended that patients are advised to limit alcohol intake.

A systematic review published in 2013 found that no randomised controlled trials had assessed dietary iron reduction and its effects on haemochromatosis management.[17] However, from available limited evidence the authors estimated that dietary iron reduction could reduce the need for venesection by one to three sessions per year, depending on patient characteristics. Therefore, dietary iron reduction may reduce clinical burden but there is no data on the longer-term effects of dietary iron reduction on prognosis.

Possible patterns of inheritance of haemochromatosis alleles*

		Genetic risk of haemochromatosis for offspring **
Two C282Y heterozygote parents	**Parents** ⬤ C282Y / – (other allele not associated with haemochromatosis) ⬤ C282Y / – **Offspring** 🔴 C282Y / C282Y ⚫ C282Y / – ⚫ – / C282Y ⚫ – / –	One in four homozygous for C282Y, at risk of hereditary haemochromatosis Two in four heterozygous for C282Y, not at risk of hereditary haemochromatosis but may pass risk to their own offspring One in four without C282Y risk alleles
One C282Y heterozygote parent **+** **one C282Y homozygote parent**	**Parents** 🔴 C282Y / C282Y ⬤ C282Y / – **Offspring** 🔴 C282Y / C282Y 🔴 C282Y / C282Y ⚫ C282Y / – ⚫ C282Y / –	One in two homozygous for C282Y, at risk of hereditary haemochromatosis One in two heterozygous for C282Y, not at risk of hereditary haemochromatosis but may pass risk to their own offspring
One C282Y heterozygote parent **+** **one H63D heterozygote parent**	**Parents** ⬤ C282Y / – ⬤ H63D / – **Offspring** 🔴 C282Y / H63D ⚫ C282Y / – ⚫ – / H63D ⚫ – / –	One in four with "compound heterozygote" genotype C282Y/ H63D. At risk of hereditary haemochromatosis, but risk is lower than C282Y/C282Y genotype Two in four heterozygous for C282Y or H63D. Not at risk of haemochromatosis but may pass risk to their own offspring One in four without risk alleles
One heterozygous parent **+** **one parent without risk alleles**	**Parents** ⬤ C282Y / – ⬤ – / – **Offspring** ⚫ C282Y / – ⚫ C282Y / – ⚫ – / – ⚫ – / –	Since condition is recessive no offspring are at risk, although two in four may pass risk to their own offspring

* The purpose of this table is to highlight common scenarios. Other combinations of parental genotypes are possible, e.g, in the rare circumstance that both parents are homozygous for risk alleles, all offspring will be genetically at risk for haemochromatosis.

** These figures represent theoretical mathematical averages. It is possible in clinical practice to find a family where siblings have a distribution of risk alleles which differs from that shown here.

Monitoring clinical complications

The range of complications and other conditions which can arise from iron overload is diverse. Particular attention should be paid to the potential development of liver disease. Clinicians should also ensure that patients with haemochromatosis have up to date hepatitis A and B vaccinations to reduce the risk of liver damage.

Haemochromatosis can result in a wide range of complications due to the deposition of iron in tissues around the body. There are no specific guidelines for monitoring all of these complications. In general, clinicians should be aware that patients with haemochromatosis may present with a variety of symptoms, and have a lower threshold for investigating other conditions. During ongoing management clinicians should be alert for the development of symptoms and signs suggestive of complications related to iron overload.

Patients with haemochromatosis are at increased risk of liver disease

The development of liver disease is one of the most pressing concerns in the management of patients with haemochromatosis. Patients are at greatly increased risk of hepatic fibrosis and cirrhosis, as well as hepatocellular carcinoma. Key points include:

- The absolute risk of liver disease in people with two C282Y risk alleles is approximately 5% for males and 1% for females[3]

- People with haemochromatosis and cirrhosis have a reduced life expectancy[6]

- Hepatocellular carcinoma is reported to account for 30% of deaths in people with haemochromatosis (very rarely without cirrhosis[10]

- Patients with hereditary haemochromatosis and cirrhosis should be screened for the development of hepatocellular carcinoma by ultrasound every six to twelve months,[10] or an alternative screening strategy discussed with a haematologist or oncologist.

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