The majority of medicine is practised after disease processes are well established and symptoms are present. It is generally felt that a more productive and cost-effective method, however, is diagnosing potential for illness before it occurs and preventing it. While it is true that not everyone with high blood pressure, diabetes, and hyperlipidemia will develop disease, the chances are very good that some ill health will result.

A common form of genetic hemochromatosis has now been added to the group of diseases which are both diagnosable and treatable in the presymptomatic phase (Table 1). Simple clinical testing and readily available genetic diagnostics have made the detection of risk in the target population available to virtually every physician. The treatment is not only beneficial, but, where regular blood donation is possible, socially responsible.

### In this article:
1. What is hemochromatosis?
2. How do you get hemochromatosis?
3. Does a genetic predisposition always produce symptomatic disease?
4. What are the pros and cons of genetic diagnosis?

### Table 1
What is hemochromatosis?

Hemochromatosis is a disorder of excessive iron stores.\(^1\)-\(^3\) Iron may be acquired in many ways and, once in the body, must be stored. Iron is toxic to some tissues and causes end organ damage:

- **Liver**-cirrhosis and potential for hepatocellular carcinoma
- **Heart**-congestive heart failure
- **Pancreas**-diabetes
- **Joints**-arthritis
- **Skin**-abnormal pigmentation (bronze or grey)
- **Pituitary**-hypothyroidism and hypogonadism
- **Testis**-impotence

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**Case Study**

A 56-year-old male presents to your office with unexplained elevation in liver function tests. As part of your investigation, you discover that the patient has an iron saturation of 93% and a ferritin of 836.
Hemochromatosis

How do you get hemochromatosis?

By genetic means: The commonest form of hemochromatosis is associated with mutations in the HFE gene. This is primarily a disorder of individuals of Northern European heritage. Rare forms of genetic hemochromatosis, including neonatal and juvenile, are associated with other genes. As well, there are genetic forms of hemochromatosis which we know exist, but the genetic cause is not yet known.

By environmental means: Individuals with chronic anemia (whether genetically caused, such as congenital hemolytic anemia, or acquired from bone marrow failure), who require frequent transfusions, can also develop iron overload. Rarely, exogenous iron in the diet can cause iron overload, such as with the African Bantus, who acquire large amounts of iron through brewing beer in iron pots. Individuals with chronic liver disease, particularly when due to excess use of alcohol, can also accumulate large stores of iron in the liver independent of any genetic predisposition.

How is HFE hemochromatosis inherited?

The HFE gene is located on chromosome 6 and was cloned in 1996. The gene product controls the rate of absorption of iron from the small bowel. There are three common alleles—normal, C282Y, and H63D. There is also a rare mutation called S65C which is clinically identical to H63D. C282Y is almost exclusively found in populations of Northern European heritage. H63D is less common and distributed fairly equally around the world.

Individuals must have two abnormal alleles to be at significantly increased risk for symptomatic hemochromatosis. Hence, hemochromatosis is an autosomal, recessively inherited disorder. Those who have the genetic constitution C282Y/C282Y have at least a 50% chance of developing one or more symptoms of iron overload if left untreated. Those who have the genetic constitution C282Y/H63D have less than a 10% chance, and those who are H63D/H63D have a risk of approximately 1% of
developing symptomatic disease. The heterozygotes (carriers), N/C282Y and N/H63D, are at little increased risk for symptomatic iron overload.

For individuals of Northern European heritage, approximately three to four out of 1,000 will have a genetic constitution which confers significant risk for iron overload disease. Another 10% to 15% will be heterozygotes.\textsuperscript{5,6} So, even though this is a recessive disorder, the high frequency of the abnormal alleles in this population can result in a family history of affected individuals in more than one generation.

Does a genetic predisposition always produce symptomatic disease?

The simple answer is no. Even among individuals born with a genetic predisposition to absorb and store excess iron, \textit{i.e.}, those with the genetic constitution C282Y/C282Y, C282Y/H63D, or H63D/H63D, not all develop symptomatic disease. This is partially due to the alleles themselves, C282Y being much more severe in effect than H63D.

However, environmental factors are also very important. Development of iron stores requires time and, usually, dangerous amounts do not accumulate until well into adulthood. Women accumulate iron slower than men, due to periodic loss of iron through menstruation and childbearing.\textsuperscript{8} Vegetarians
Figure 1. Clinical suspicion of HFE hemochromatosis.

HFE: gene for hereditary hemochromatosis
Fe: iron
Sat: saturation
N: normal
↑: elevated
acquire less iron through food than heavy meat eaters. Iron supplements, a component in the majority of multivitamin preparations, may add to stores, while regular blood donations deplete.

There are additional genetic and acquired factors which can influence end organ damage. Coincident risks to the liver, such as excessive alcohol use or chronic viral hepatitis, can accelerate the onset of liver damage in a person with a genetic predisposition to hemochromatosis.6

Table 2
Who is most at risk?

1. First-degree relatives of those with definitely diagnosed HFE hemochromatosis. Siblings of an affected individual are at 25% risk of having the same genetic constitution. Offspring are at least obligate carriers, but may also be at risk for a significant genetic constitution if their affected parent has, by chance, married a carrier.

2. Individuals with unexplained abnormalities suggestive of end stage organ damage from excessive iron stores, especially liver function abnormalities. Remember there are many more common causes of cirrhosis, congestive heart failure, diabetes, arthropathy, skin discoloration, and endocrine insufficiencies.

3. It is controversial whether individuals of Northern European heritage should be screened in middle age in the same way that one screens for hypertension, diabetes, and hyperlipidemia.10 One school of thought feels that this is a preventable disorder and, therefore, general screening should be done in the target population. The other school feels that too few individuals with genetic predisposition develop serious end organ disease to justify population screening.

Who can I refer to?
For patient support group:
Canadian Hemochromatosis Society
#272, 7000 Minoru Blvd
Richmond, BC V6Y 3Z5
Toll Free 1-877-BADIRON
Fax: (604) 279-7138
Web site: http://www.cdnhemochromatosis.ca

For specialist assistance:
• Medical genetics clinics
• Hematologists
• Subspecialists appropriate to specific end organ disease

Helping Keep Your Patients Covered.
Hemochromatosis

How can I screen for hemochromatosis?

A high index of suspicion is essential, as none of the end organ disorders are pathognomonic for hemochromatosis. Studies have shown that, prior to diagnosis, the only significant historical and physical differences between those with genetic predisposition and those without, is an excess of liver function abnormalities amongst the former. The most obvious clue is a family history of a definitively diagnosed case. Other occurrences which should raise high suspicion include unexplained cirrhosis or liver cancer (Table 2).

The best objective laboratory screen is the percent transferrin saturation. A saturation > 60% in males or > 50% in females is suspicious for hemochromatosis. An elevated ferritin in the setting of elevated percent transferrin saturation adds further suspicion. Elevated ferritin by itself is not an appropriate screening tool, as ferritin is an acute phase reactant and may be elevated in acute or chronic infectious, inflammatory, or neoplastic conditions. The hemoglobin and hematocrit are useful only in timing of phlebotomies. Hemochromatosis does not cause polycythemia.

What are the pros and cons of genetic diagnosis?

The major advantage of genetic diagnosis is the opportunity to practice preventive medicine. An individual with the genetic predisposition to develop end organ damage will not do so if iron stores are kept to normal levels. Even symptomatic disease can be improved somewhat, although the risk for hepatocellular carcinoma cannot be removed if liver damage has already occurred.

The major disadvantage is a risk of discrimination with respect to life and disability insurance for anyone diagnosed presymptomatically with a genetic predisposition. This could conceivably affect ability to emigrate or to obtain health-care insurance, should one move outside of Canada (Tables 3,4).

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Who should have the genetic test?</th>
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<tbody>
<tr>
<td>1. First-degree relatives of individuals with definitely diagnosed HFE hemochromatosis.</td>
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<tr>
<td>2. Those with per cent transferrin saturation levels at or above levels of suspicion, particularly if they also have elevated ferritin.</td>
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<th>Table 4</th>
<th>What about genetic counselling?</th>
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<td>Before any molecular diagnostic test is done, the patient must be fully informed of:</td>
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<tr>
<td>1. The limitations of the test. In this case, the only genetic condition that will be diagnosed is HFE hemochromatosis. This is the only genetic test for hemochromatosis currently available and it will not diagnose other types of genetic or acquired hemochromatosis. Nor can the genetic test predict who specifically will develop end organ disease, of what type, at what age, or of what severity.</td>
<td></td>
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<tr>
<td>2. The pros and cons of testing must be clearly outlined, particularly with risk of discrimination. Testing of minors is not done, as iron overload is rare in this age group and potential for discrimination outweighs benefit.</td>
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</tbody>
</table>
Treating HFE hemochromatosis

In patients with significant genetic predisposition (i.e., C282Y/C282Y, C282Y/H63D and H63D/H63D), it is recommended to reduce ferritin levels to between 20 and 50, while maintaining hemoglobin above 110. Initially, phlebotomy should be done every one to two weeks. The frequency will vary with each individual.

If the patient has no evidence of significant end organ damage and is not otherwise ineligible to be a blood donor, regular donation (every eight weeks) at the Canadian Blood Services is recommended. HFE hemochromatosis is not infectious. Routine blood donation may be adequate for patients whose hemochromatosis is discovered early, but more advanced cases may initially require more frequent phlebotomy (Table 5).

Is a liver biopsy necessary?

A liver biopsy is no longer necessary to make the diagnosis of HFE hemochromatosis. However, it may still be necessary to stage the degree of liver damage or to diagnose hepatocellular carcinoma. For cirrhosis not due to HFE hemochromatosis, liver biopsy is necessary to make the correct diagnosis.

Table 5
Any other recommendations?

1. Reduce exogenous iron in the diet:
   - Avoid dietary supplements with iron.
   - Reduce red meat and other foods containing iron.
   - Avoid cooking in uncoated iron pots and pans
2. Reduce coincident risks to end organs, especially excessive alcohol

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Hemochromatosis

How do I treat specific end organ disease/failure?

Phlebotomy to appropriate ferritin levels will produce improvement in some symptoms in most individuals, but is not totally predictable. Specific end organ disease should be treated as per usual protocols for cirrhosis, diabetes, heart failure, hypothyroidism, etc.

Take-home message

Genetic hemochromatosis due to mutations in the HFE gene is both diagnosable and treatable, with tangible prevention of future morbidity and mortality. However, in order to use resources intelligently, it is important to appreciate:

- the target at-risk group;
- the differential diagnosis of iron overload; and
- the sequential approach to diagnosis and management.

References: