

Hereditary Hemochromatosis

Why is Hereditary Hemochromatosis (HH) an emerging public health issue?

As a common genetic disorder with simple, effective treatment, hemochromatosis offers a model for other genetically influenced chronic diseases that some day may have interventions to improve prognosis. Population screening for hemochromatosis using the transferrin saturation test has been advocated by some experts to permit the initiation of therapeutic phlebotomy (the incision of a vein for the purpose of removing blood from the body) before the onset of some health complications. However, this view is not universal (see report of the working group Iron overload, public health, and genetics. *Ann Int Med* 129:921-96).

Hemochromatosis is one of the most common known genetic disorders in the United States Caucasian population and is a treatable condition. Approximately 1 in 200-400 people in the United States has hemochromatosis. Between one in eight and one in every ten people in the general population have the [gene](#).

Despite the high prevalence of hemochromatosis, most cases go undiagnosed. The symptoms are often confused with other conditions. This enforces the need for increased knowledge about the disorder. Routine screening for adults appears to be cost effective and the condition is treatable. Suggested reading: Cogswell ME, McDonnell SM, Khoury MJ, Franks AL, Burke W, Brittenham G (1998) Iron overload, public health, and genetics: evaluating the evidence for hemochromatosis screening. *Ann Intern Med* 129:971-9 [[Medline](#)]

What is HH?

Hemochromatosis (He-mo-chro-ma-toe-sis) is commonly known as iron overload disease. It is a treatable disorder where excessive amounts of iron are absorbed and subsequently accumulates in body tissues. The accumulation of iron damages body organs, especially the pancreas, liver and heart. Excess iron may be removed thereby preventing the progression of HH.

Hemochromatosis occurs in men and women equally and among all age groups including children. HH has been reported in all races. Primarily Caucasians, especially of Irish, Scottish, Celtic, or British (Northern European) heritage, have a higher risk for the hemochromatosis gene change.

The diagnosis of hereditary hemochromatosis is based on a combination of clinical, laboratory, and genetic studies. Patients with hemochromatosis may have some or all of the characteristic features.

What are the symptoms of HH?

Most symptoms of hemochromatosis are nonspecific, making it difficult to diagnose. The most common symptoms include arthritis and joint pain, chronic fatigue, weight loss, frequent cold and flu-like symptoms, infections, and abdominal pain. Diabetes, heart disease, cirrhosis and cancer of the liver, hypothyroidism, and high concentrations of liver enzymes often occur as the disease progresses. Impotence in men and early menopause or irregular menses in women may also be symptoms. Also common is a graying or bronzing of the skin due to deposits of iron in the skin. Signs and symptoms of hemochromatosis most often appear between the ages of 40 and 60 in males and after menopause in females. Symptoms can, however, develop by the age of 20. Cases

of people as young as two years of age with symptoms have been reported. Symptoms usually do not occur until iron accumulation in body organs has reached a degree where damage becomes noticeable.

If diagnosed and treated early, life expectancy for individuals with HH is normal. Since the signs of HH do vary and are similar to other diseases, early detection is crucial. Once symptoms have appeared, tissue damage may have occurred which may not be reversible. Treatment may prevent further tissue damage.

Family history information and physical examination

If HH is suspected in an individual, a complete family and medical history is obtained. The history typically includes:

- a review of current and past health problems, such as a history of liver, joint, heart disease, diabetes mellitus, fatigue, sexual function, and skin pigmentation,
- a dietary history focused upon general dietary habits and food choices, use of dietary supplements, ingestion of alcohol,
- history of blood donation, receipt of blood transfusion, and illness associated with blood loss,
- details of menstruation, childbirth, lactation, menopause, and hysterectomy.
- it is important to note contraceptive use because women taking contraceptives may have decreased menstrual blood loss or may absorb less dietary iron,
- inquiries about family members, especially first-degree relatives (brothers, sisters, parents, and children), for a possible history of HH related symptoms.

A physical examination will include assessments of the liver, joints, heart, endocrine status, and skin pigmentation.

Once an individual has been diagnosed with HH, all blood relatives (not just immediate family) of the HH individual should be offered screening of HH immediately. Siblings of individuals with this disorder have a 25% risk of being diagnosed with HH themselves. Children of individuals with HH have 50% chance of being affected. Screening should be repeated annually. There is still no general consensus on what age to screen children.

What causes HH?

Primary or hereditary hemochromatosis is [inherited](#), but there are some cases where HH is caused by other factors. The non-hereditary form is referred to as secondary HH. Secondary HH results from blood transfusions ("induced iron overload") or excessive dietary iron intakes. Secondary HH can also occur as a side effect of other disorders.

Hereditary hemochromatosis (HH) is inherited in an [autosomal recessive](#) fashion. Individuals who carry one gene responsible for HH are called carriers or [heterozygotes](#) and usually have no symptoms of HH. Occasionally a carrier will manifest symptoms of HH. However, those individuals having two copies of the HH gene, called [homozygotes](#), usually demonstrate features of the disease. The diagnosis may be complicated since there have been reports of both

individuals who have two HH gene changes and yet have no symptoms and reports of individuals with only one HH gene having symptoms.

When two carriers (heterozygotes) have children, the risk is 1 in 4 or 25% their children will have homozygous HH (two HH genes); 25% their children will have no HH genes; and 50% their children will be carriers like themselves (have one HH gene).

How is HH detected?

Laboratory testing consists of general lab tests such as transferrin saturation or serum ferritin tests and/or genetic (DNA) studies. A liver biopsy may also be performed to confirm the diagnosis of HH.

Transferrin saturation test

The most common and useful screening for hemochromatosis is a random transferrin saturation (TS). If the test comes back elevated, then a second test is repeated after an overnight fast. Persistently elevated transferrin saturation is the earliest manifestation of HH. However, not all individuals with high transferrin saturation values have this disorder.

Traditionally, a fasting transferrin-iron saturation of 60% or more for men and 50% or more for women on at least two occasions in the absence of other known causes of elevated transferrin-iron saturation has been considered suggestive of HH. Recent studies indicate that a threshold transferrin-iron saturation of 45% may be more sensitive, but less specific, for detecting HH. Below are the current values suggestive of hemochromatosis.

	Transferrin-iron Saturation Values
Men	60% or more
Women	50% or more
Safe Range	12% to 45%

Table 1. Transferrin-iron saturation values currently indicative of hemochromatosis. Values for men and women and those in the saferange are given.

Serum ferritin

To assess the presence of iron overload, serum ferritin is also measured. Although serum ferritin concentration increases progressively over time in untreated patients with HH, it is not specific for HH and cannot be used alone in identification of individuals with HH. The serum ferritin level defines the point at which treatment should be initiated.

	Serum Ferritin Concentration
Men	>300 mg/L
Women	Premenopausal > 200 ug/L
	Postmenopausal >300 mg/L
Safe Range	15-150

Table 2. Serum ferritin concentrations currently indicative of hemochromatosis. For comparison, safe serum ferritin concentration range is given.

DNA testing

Indications for DNA testing include (see JAMA 280:172-78, 1998):

- previous clinical diagnosis of HH,
- positive family history or partner with two identified HH gene changes,
- elevated transferrin saturations and serum ferritin levels,
- unexplained elevation of serum liver enzymes, cirrhosis, liver failure, liver cell tumors, and diabetes.

Genetic testing for gene changes ([mutations](#)) plays an important role in confirming the diagnosis of HH. Gene testing is also useful in helping to resolve uncertain cases.

The gene for HH is located on [chromosome](#) 6 that codes for the [protein](#), hereditary hemochromatosis protein, HFE. Currently, C282Y and H63D are two genetic changes found to be linked with HH. A few other gene changes have been identified. The C282Y gene change occurs most frequently.

% of Patients with HH	Associated Gene Change
~60-90%	C282Y / C282Y
~3%	C282Y / H63D
~1%	H63D / H63D
~4%	H63D / ?
~1%	C282Y / ?
~6%	? / ?

Table 3. Percentages of Patients with Gene Change Combinations. Percentages vary with Populations Studied. From [Ramrakhiani and Bacon \[1998\]](#)

About 12%-15% of individuals who are clinically iron overloaded may have a negative result on the DNA test. These individuals may have another HH gene change that has yet to be discovered

or other disease determinants that we do not yet understand. By having a DNA test, one can discover if they have the single or double gene change for HH.

Liver biopsy

Liver biopsy with tissue evaluation and determination of hepatic iron concentration has long been the "gold standard" or the most accurate test for the diagnosis of HH. However, emphasis on early detection before symptoms occur has called into question the need for liver biopsy in evaluating the early stages of HH. Nonetheless, many experts believe that liver biopsy is still central to the evaluation of most patients. It is used to confirm iron overload by directly measuring the amount of iron per gram of liver tissue and the presence of liver damage.

It is generally agreed that liver biopsy is essential for patients who present with cirrhosis or with a history of excessive alcohol intake. Definitively excluding cirrhosis is important because HH patients with cirrhosis have a greater than 200-fold increased risk of developing tumors of the liver.

How is HH treated?

The degree of organ damage from iron overload at the time of diagnosis is a major determinant of a person's prognosis and treatment. For patients that do not have tissue or organ damage, long-term outcome and life expectancy with proper management of the disease equals that of people who do not have iron overload.

Phlebotomy is the customary and preferred treatment for hemochromatosis. Phlebotomy is safe, efficient, and economical. Giving blood regularly alleviates iron build up and helps to maintain low normal body iron stores. When phlebotomy is applied before iron overload becomes severe, complications, such as organ damage, can be prevented. Patients already experiencing signs and symptoms might have a complete reversal of some but not all symptoms when treatment is applied. However, damage usually can not be reversed. Some complications may not be improved by phlebotomy. Cirrhosis of the liver due to iron overload, joint disease and significant improvement in joint function, hypogonadism, and thyroid disorders are rarely alleviated. The purpose of phlebotomy is to induce a mild anemia and maintain it until the storage iron is greatly reduced. The series of phlebotomy sessions should not be discontinued until deironing has been completed.

Phlebotomy should be initiated in men and women with serum ferritin levels of 200ug/L or more, regardless of the presence or absence of symptoms. Treatment should not be delayed until symptoms develop. Age is never a reason to disqualify someone from treatment, but rarely do children and adolescents have severe iron overload and need aggressive phlebotomy. Frailty, small-stature, and extremely old or young may require the adjustment in the amount of blood removed, but never the frequency. Mild anemia may even qualify someone for phlebotomy. For the first year, deciding how often to give blood is often a matter of trial and error. The frequency of phlebotomy is determined individually for each patient based on symptoms and levels of hemoglobin (the protein serving to convey oxygen to the tissues) and serum ferritin. The initial phase of treatment usually involves 1 unit of whole blood (250-500 mg of iron) being removed 1-2 times weekly until the serum ferritin levels reach 10-20 ng/ml. This is called the "de-ironing phase". This continues until all stored iron is removed as indicated by monitoring hemoglobin and serum ferritin levels. This can take from one month to three years to occur. The second phase of treatment involves the long-term maintenance of serum ferritin levels at 50 ng/ml or less thereafter by periodic removal of blood. This usually requires removal of 3-5 units of whole blood annually. Maintenance must be continued throughout the life span.

Blood Banks in the United States do not use blood donated by HH individuals. HH individuals are not considered volunteer donors since they require phlebotomy for treatment. However, the US Food and Drug Administration (FDA) ruled in August of 1999 that Blood Banks can now file for a variance to use hemochromatosis blood as donor blood and to treat HH patients for free. Iron chelation, the binding of iron to form a substance that will dissolve in water, is seldom recommended. This treatment lacks the effectiveness of phlebotomy. Some dietary restrictions are issued in addition to clinical treatment. These restrictions are usually unnecessary unless a patient is unable to tolerate phlebotomy. Guidelines include avoiding medicinal iron, mineral supplements, food fortified with iron such as breakfast cereals, excess vitamin C, and uncooked seafood (i.e. oysters). Consuming in moderation foods that contain large concentrations of iron available to the body, such as red meats and organ meats, and not using iron cookware is also recommended. A low iron diet is not recommended as high iron foods also contain other nutrients needed for good nutrition.

Information and Support Resources

- [GeneClinics](#)
- Centers for Disease Control-HH
 - [Screening for Hereditary Hemochromatosis](#)
 - [Overview of Hemochromatosis](#)
- [NIH: National Institute of Diabetes and Digestive and Kidney Diseases \(NIDDK\)](#)
- [American Hemochromatosis Society](#)
- [Iron Disorders Institute](#)
- [Iron Overload Diseases Association, Inc](#)