Canadian HEMOCHROMATOSIS SOCIETY
Société canadienne de l'hémochromatose

Hemochromatosis – Diagnosis / Testing

Transferrin Saturation and Serum Ferritin Tests

Currently, **tests for hemochromatosis are not part of a general medical checkup**. They must be specifically ordered on a blood lab requisition form. A doctor can order an iron series profile and, depending on the lab, may include serum iron, ferritin, transferrin, and transferrin saturation or total iron binding capacity. Of particular importance in this profile is serum ferritin (SF) and transferrin saturation (TS). These tests should ideally be performed in the morning after the patient has fasted overnight for a more accurate reading.

Serum ferritin and transferrin saturation measurements reflect how much iron is in the body and how much is being transported and stored.

Biochemical Blood Screening Tests

Serum Ferritin (SF)

A normal serum ferritin result varies with gender and age. An abnormally high ferritin will be highlighted on the lab test result as out of range. Ferritin is a non-specific test and can be elevated for reasons other than hemochromatosis. Subsequent tests may be necessary to see if elevations continue over time. A level of more than 200 ng/ml for women and 300 ng/ml for men is considered out of range, but it is rare for organ damage to occur with ferritin levels below 1000 ng/ml.

Transferrin Saturation (TS)

A normal result is typically 25-40% saturation. **Anything greater than 45% saturation requires further investigation**. Transferrin saturation is more specific to hemochromatosis but is still considered a screening test and on its own does not confirm hemochromatosis.

If both serum ferritin and transferrin saturation come back abnormally high, or even high normal, these screening blood tests may be repeated for accuracy. If the results continue to be elevated, then further medical work-up is required. Additional diagnostic testing can be done to confirm the presence of hemochromatosis. This includes genetic testing for the HFE gene.

Elevated levels of serum ferritin and transferrin saturation can be detected even before symptoms are noticeable. **Continued abnormally high results of serum ferritin and transferrin saturation are called biochemical iron overload and is considered the first sign of hemochromatosis**.

Genetic Diagnostic Test

Genetic testing of the HFE gene will confirm the diagnosis of hemochromatosis. A blood sample is taken for the genetic test which checks the HFE gene for the mutations C282Y and H63D, the ones abnormal in Type I HFE- Hemochromatosis.

Possible **positive combinations** resulting from the HFE genetic test:

> **C282Y / C282Y** - homozygous for HFE Type I Hemochromatosis. The majority of hemochromatosis individuals have this combination, with severe biochemical iron overload occurring in most if not all of the individuals.

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C282Y / H63D - compound heterozygous for HFE Type I Hemochromatosis. Significant iron overload occurs in only 15% of these individuals. In the other 85%, the iron overload is generally much less severe.

H63D / H63D - homozygous for HFE Type I Hemochromatosis. Iron overload is unusual, with not much chance of organ damage, although other (genetic and environmental) factors may play a role.

A positive HFE genetic test will implicate other family members who should also be tested. First-degree relatives (parents, siblings, and children) are at risk of being carriers of the HFE gene, or inheriting both abnormal copies of the HFE gene and developing hemochromatosis. Spouses should be tested if there are minor children, so as to assess their risk. Genetic counseling may be helpful, especially for those found to be positive who are contemplating starting a family.

See Genetic Inheritance at www.ironoverload.ca/disorder/inheritance.php for graphical representations of possible inheritance.

If the genetic test is **negative** because mutations (C282Y and H63D) were not detected in the HFE gene, then there may be another reason for iron overload, such as another disease, or another form of hemochromatosis caused by a different gene. Further medical investigation will be required. Hepatitis C, chronic alcoholism and those with a fatty liver are all at risk of developing mild to moderate secondary iron overload.

Other Possible Tests

In addition to the biochemical blood screening tests (ferritin and transferrin saturation) and the genetic HFE test, there are other tests that can be ordered to help assess risk of, and monitor, injury to particular organs:

A **liver enzymes test** is often performed to analyze ongoing liver injury. Liver enzyme measurements are
typically followed to see that they return to normal with de-ironing. If not, they must be explained. For example, cirrhosis may already be present, or the patient may have another liver disease.

A **liver biopsy**, to establish the degree of damage to the liver, may occasionally be done, but is not necessary for establishing the diagnosis in the majority of patients with hemochromatosis. It is not helpful for ongoing monitoring.

Radiological imaging of the liver is usually required; it gives a structural picture of the liver and may be useful in finding cirrhosis and some of its complications. Most importantly, in patients with cirrhosis, it is used to screen for primary liver cancer (hepatoma / HCC), a complication that occurs in about 25 per cent of patients with cirrhosis resulting from hemochromatosis. Most patients should be enrolled in a program for hepatoma screening consisting of an alpha-fetoprotein (a blood test) and a radiological procedure, usually an ultrasound or triphasic CT scan, every six to twelve months.

Additionally, all patients should be screened for **other causes of hepatitis**, and those without protection should be vaccinated for hepatitis A and B.

Medical Services Plan Testing Policy

The BC Government's Medical Services Plan website outlines clinician hemochromatosis testing guidelines and protocols. Please visit www.hlth.gov.bc.ca/msp/protoguides/gps/ironoverload.pdf .