

KEY FEATURES TO IDENTIFY INDIVIDUALS AT RISK OF HEREDITARY HEMOCHROMATOSIS (HH) AND CANDIDATES FOR GENETIC TESTING

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POINT OF CARE TOOL

Jan 2026

More on HH here



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DEEP DIVE

A positive family history even in the absence of symptoms



Sustained elevation on multiple occasions of serum transferrin saturation (TS), serum ferritin (SF) levels, or aminotransferase levels (ALT) in the absence of symptoms*



*TS >45% and SF >300ug/L in men and post-menopausal women or >200ug/L in pre-menopausal women

ALT can be elevated in up to 14% of the general population. If ALT is elevated, consider ordering SF and TS. If those are also elevated then consider genetic testing.

The presence of symptoms, especially two or more, particularly liver disease or arthritis




Mean red-cell volume >94 fL



Symptoms and clinical features of HH:

- Weakness, chronic fatigue
- Abdominal pain, weight loss
- Arthropathy (especially metacarpophalangeal joints, hips, knees)
- Diabetes
- Hepatomegaly
- Cirrhosis
- Primary liver cancer (hepatocellular carcinoma, cholangiocarcinoma)
- Hypogonadotropic hypogonadism (decreased libido and impotence in males, amenorrhea in females)
- Cardiomyopathy, arrhythmias
- Progressive increase in skin pigmentation

 Genetic testing for HH is performed in a specialized hospital laboratory (molecular) on a blood sample. The blood sample can be obtained at any community lab. Contact [your local genetics centre](#) to ask about genetic testing in your region.

General population screening for HFE-hereditary hemochromatosis is not recommended as the disease penetrance is low.

Children do not require genetic testing for HH as it is an adult onset condition.

For screening and surveillance recommendations for those with positive genetic test results, see the next page or read more about hereditary hemochromatosis at www.geneticseducation.ca

 Public resource

- Canadian Hereditary Hemochromatosis Society
 - <https://www.toomuchiron.ca/>

SURVEILLANCE AND MANAGEMENT RECOMMENDATIONS FOR INDIVIDUALS WITH A POSITIVE GENETIC TEST RESULT FOR HEREDITARY HEMOCHROMATOSIS (HH)

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Genotype

(genetic test result, *HFE* gene variants detected)

Associated risk of iron overload

C282Y/C282Y

- Highest risk of developing iron overload (38-50%)
- 10-33% of individuals with iron overload will develop related symptoms

C282Y/H63D

0.5-2% lifetime risk of developing iron overload

Other genotypes are possible i.e. C282Y/S65C, H63D/H63D, S65D/S65C but are not considered clinically significant or at increased risk for iron overload. Additional genetic testing for non-*HFE* related hemochromatosis is not recommended.

Individuals with positive genetic testing and/or family history who are asymptomatic

Transferrin saturation (TS) and serum ferritin (SF) levels should be measured in these individuals. If elevated (i.e. TS (>45%) and SF are elevated (>300ug/L in men and post-menopausal women; >200ug/L in pre-menopausal women)), further workup should proceed as outlined below. In homozygous individuals (C282Y/C282Y) with a normal SF at diagnosis, ongoing monitoring of TS, SF and liver aminotransferase every 5 years should be considered to detect progression.

Treatment of iron overload

Therapeutic phlebotomy, which is both safe and effective, is the mainstay of treatment for iron overload. With treatment, many complications can be avoided. Treatment is usually indicated in the presence of biochemical evidence of iron overload (i.e. TS >45% AND SF are elevated (>300 ug/L in men and post-menopausal women; >200 ug/L in pre-menopausal women) or clinical manifestations e.g. end-organ damage. A SF of 1000 ug/L or greater significantly increases morbidity. A genetic predisposition to iron overload (e.g. C282Y/C282Y genotype) is not, on its own, an indication for treatment in the absence of abnormal iron indices.



After initial treatment, maintenance therapy is performed to keep SF levels and hemoglobin within the normal range. Maintenance therapy typically involves phlebotomy approximately every three months; however, the frequency varies widely and should be tailored to each patient's individual needs.

Individuals should also be advised to avoid consuming raw seafood to minimize the risk of *Vibrio vulnificus* infection (a bacteria that thrives on iron), to limit alcohol intake to decrease the likelihood of advanced liver fibrosis, and to avoid cast iron cookware and vitamin C supplements. Dietary iron modification does not significantly alter SF levels and is not a substitute treatment for individuals with iron overload. Individuals with two *HFE* gene pathogenic variants should consider the hepatitis A&B vaccines.

Liver

Individuals with advanced liver fibrosis should undergo routine liver ultrasonography cancer surveillance at 6-month intervals

With early identification of at-risk individuals, appropriate surveillance of iron indices, and treatment when necessary, many complications can be avoided.

Read more about hereditary hemochromatosis

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