5 RED FLAGS TO IDENTIFY THOSE AT RISK OF HFE-HEREDITARY HEMOCHROMATOSIS MOST LIKELY TO BENEFIT FROM GENETIC TESTING

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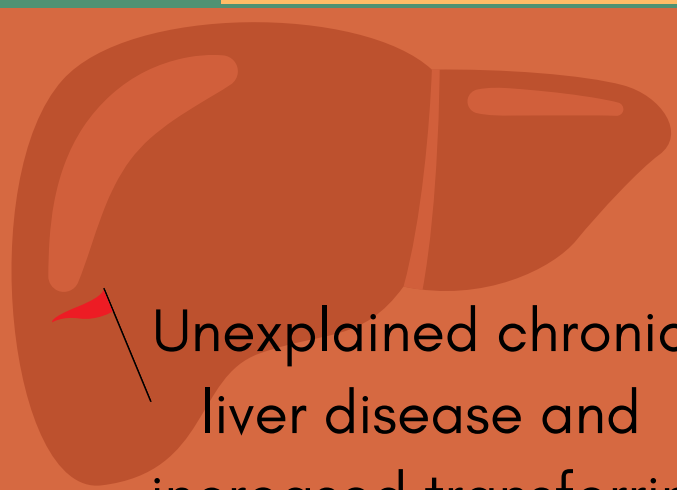
POINT OF CARE TOOL

May 2023

Biochemical evidence of iron overload (>45% fasting transferrin saturation and >300 ug/L serum ferritin in men and post-menopausal women or >200 ug/L in pre-menopausal women.)

Biochemical evidence of iron overload will be present before the onset of symptoms.



Unexplained chronic liver disease and increased transferrin saturation.

Elevation of ferritin alone is not necessarily due to iron overload. Ferritin is an acute phase reactant and can be elevated due to infection, inflammation and malignancy.

Individuals with hereditary hemochromatosis occasionally demonstrate a normal transferrin saturation and an elevated ferritin. If clinical suspicion is high and/or the patient has a family history of hemochromatosis, genetic testing is still warranted.

An adult with a first-degree relative (*sibling, parent or child*) where genetic testing identified C282Y homozygosity

i.e. the individual has two copies of the C282Y variant, one in each copy of their *HFE* genes C282Y/C282Y

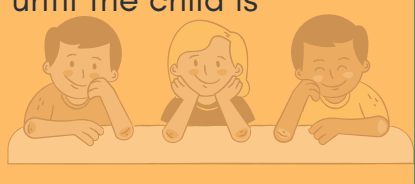
A symptomatic adult with a first-degree relative where genetic testing identified **at least one copy** of the C282Y variant

A family history suggestive of hereditary hemochromatosis e.g. iron overload, and/or liver disease, type II diabetes, arthritis, heart disease, particularly when two or more are present in an individual

Genetic testing for hereditary hemochromatosis is performed in a specialized hospital laboratory on a blood sample. Many genome diagnostic laboratories prefer that you attach their requisition to the provincial ministry of health requisition. To find your local genetic testing laboratory click here.

Children do not require genetic testing for hereditary hemochromatosis.

- Cost savings have been reported when the unaffected parent undergoes genetic testing first, to better asses a child's risk.
- If the unaffected parent's genetic test result is negative, genetic testing of children would not be indicated.
- If the genetic test result is positive, testing would not be offered until the child is 18 years of age.



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

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

Additional resources on hereditary hemochromatosis are:

- Clinical guidelines
  - Kowdley et al. Am J Gastroenterol 2019. PMID: 31335359
- Patient and clinician resources
  - Canadian Hereditary Hemochromatosis Society
  - https://www.toomuchiron.ca/

SCREENING AND SURVEILLANCE RECOMMENDATIONS FOR INDIVIDUALS WHO HAVE A POSITIVE GENETIC TEST RESULT FOR HEREDITARY HEMOCHROMATOSIS

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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%) • Many of these individuals never accumulate enough iron to cause disease ◦ About 10-33% will develop hereditary hemochromatosis-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 nor at increased risk for iron overload. Additional genetic testing for non-*HFE* related hemochromatosis is not recommended.

Screening recommendations for genotypes C282Y/C282Y and C282Y/H63D

Annual monitoring of transferrin saturation and serum ferritin

If elevated, consider referral to a specialist (gastroenterologist/hematologist) to be assessed for complications and consideration of treatment

"Elevated" is commonly defined as:

- Transferrin saturation greater than 45% **AND**
- Serum ferritin greater than 300 ug/L in males and post-menopausal females or greater than 200 ug/L in pre-menopausal females

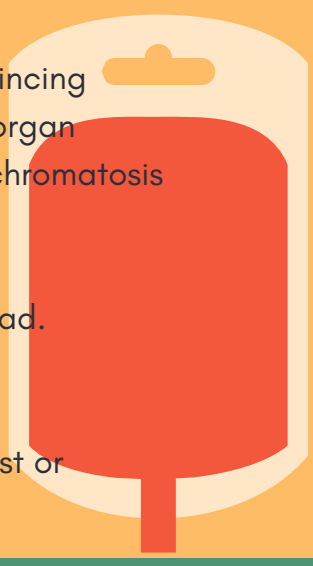
Screening recommendations for relatives

Adult family members, particularly first degree relatives, should be screened for hereditary hemochromatosis.

Genetic testing is reported to be more cost effective that annual serum iron studies. Genetic testing can be ordered through your local molecular genetic diagnostic laboratory. On the requisition include the affected relatives genotype, relation to your patient and any additional information to assist the laboratory in accurate analysis (e.g. affected relative's name, date of birth).

Screening of children is not recommended until age 18 years.

Treatment of iron overload



Therapeutic phlebotomy treatment is recommended when iron indices show convincing evidence of iron overload in a patient who is symptomatic, has evidence of end-organ damage and/or has a family member with iron overload due to hereditary hemochromatosis HH. Treatment in other circumstances may also be appropriate.

Phlebotomy is safe and effective, and is the mainstay of treatment for iron overload. The goal is to achieve serum ferritin levels between 50 and 100 ug/L

Treatment is usually initiated and monitored by a specialist (e.g. gastroenterologist or hematologist).

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 at www.geneticseducation.ca

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