



HFE-Associated Hereditary Hemochromatosis Investigations and Management

Effective Date: April 15, 2013

Scope

This guideline provides recommendations for the biochemical investigation, genetic testing and management of *HFE** associated hereditary hemochromatosis (*HFE*-HH) in adults aged > 19 years. The objectives are the early identification and management of individuals at risk for iron overload caused by *HFE*-HH.

Key Recommendations and Updates

- Screening the general population is not recommended.
- Testing non-Caucasians for *HFE*-HH is not recommended.
- Ferritin, rather than transferrin saturation, is measured as the initial marker of hemochromatosis and to determine if further testing is warranted.¹
- Revision of criteria for genetic testing of first-degree family members of individuals with *HFE*-HH.
- Discontinuation of testing for the H63D variant in *HFE*.

Diagnosis

► Differential Diagnosis

Iron overload occurs when iron absorption exceeds physiological requirements or when iron derived from repeated blood transfusions or excessive ingestion overflows normal body iron stores. Excess iron is deposited in the organs, leading to parenchymal damage and organ dysfunction. Iron overload may result from either inherited or acquired disorders.

► Inherited

The common form of hereditary hemochromatosis is due to a (C282Y) mutation in a gene called *HFE* - a mutation which occurs predominantly in Caucasians, and leads to excessive absorption of dietary iron. *HFE*-associated hereditary hemochromatosis (*HFE*-HH) is an autosomal recessive disorder and therefore, both alleles of *HFE* must be abnormal for risk to occur (1 in 230 in Caucasians is homozygous for the C282Y mutation).^{2,3} Notably, however, fewer than 10% of C282Y homozygotes develop clinical manifestations.¹

There are other rare genetic conditions leading to iron overload for which genetic testing is not available. For example, Asians with elevated ferritin are very unlikely to have *HFE*-HH⁴ and a number of mutations in other iron related genes have been identified in this population.⁵ These rare disorders are outside the scope of this guideline; suspected cases should be referred to a specialist.

► Acquired (Outside the scope of this guideline)

- transfusion dependent anemias
- various liver diseases
- anemia from ineffective erythropoiesis
- excessive ingestion of medicinal iron

* The *HFE* gene encodes the hereditary hemochromatosis protein. *HFE*-HH refers to *HFE*-associated hereditary hemochromatosis. For this guideline the condition will be referred to as hemochromatosis.

Signs and Symptoms

Because hemochromatosis can lead to gradual damage in a number of organs over many years, its symptoms can be confused with those of much more common diseases, such as alcoholic liver disease, diabetes, and osteoarthritis. If untreated, hemochromatosis can cause serious disease and premature death. Pre-symptomatic detection and treatment can completely prevent clinical sequelae and, in symptomatic patients, phlebotomy effectively reduces morbidity and mortality.^{2,3}

► Table 1: Consequences of Iron Storage by Organ

Iron Storage	Consequences
Liver	Enlargement, progressing to cirrhosis and predisposing to hepatocellular carcinoma
Heart	Congestive heart failure and/or arrhythmia due to cardiomyopathy
Pancreas	Diabetes - difficult to control type 2
Skin	Increased skin pigmentation; association with porphyria cutanea tarda
Hair	Hair loss
Joints	Arthritis, classically involvement of MCP and proximal IP joints of thumb, index and middle fingers; chondrocalcinosis
Pituitary	Hypogonadism and hypothyroidism
Testes	Hypogonadism

Most patients with hemochromatosis develop only one or a few of the above problems, with liver involvement and enlargement being the most common, occurring in most affected patients. Patients are often not diagnosed until aged > 40 years in males and even later in females. However, nonspecific symptoms such as arthralgias, fatigue, and abdominal pain may be noted years before organ dysfunction becomes apparent.

Significant end-organ damage is rare with a ferritin value < 600 µg/L. The routine complete blood count (CBC) is normal in hereditary hemochromatosis.

Testing

HFE-HH is diagnosed upon demonstration of increased iron stores (with or without clinical symptoms) **and** C282Y homozygosity.

► Whom to Test

A. Individuals of Caucasian ethnicity with signs and symptoms that might be caused by iron overload. These include:

- enlarged liver, unexplained persistent elevation of liver enzymes, cirrhosis
- arthritis (including premature osteoarthritis and classic arthropathy of thumb, index and middle fingers)
- unexplained congestive heart failure or cardiomyopathy
- adult-onset, brittle diabetes
- hypogonadism
- increased skin pigmentation

Test to Order: Ferritin (hemochromatosis)

Serum ferritin reflects total body iron stores, and a serum ferritin ≥ 600 µg/L provides a sensitive indicator of patients at risk for clinical manifestations of hemochromatosis¹ warranting follow-up genetic testing. Ferritin levels that are elevated but < 600 µg/L are less specific due to ferritin fluctuation as an acute-phase reactant.[†] In these cases genetic testing will proceed only when the transferrin saturation is *also* elevated. Transferrin saturation alone lacks both sensitivity and specificity as an indicator of hemochromatosis.⁸

[†] Ferritin is both a maker of intracellular iron stores and an acute phase reactant. Aside from *HFE*-HH, some common causes of elevated ferritin include inflammation, liver disease, dysmetabolic hyperferritemia⁹, transfusional iron overload, and non-*HFE* related genetic iron overload. Serum ferritin values may vary between laboratories and with patient age and gender. Refer to the normal reference interval provided by your local laboratory.

B. Individuals of Caucasian ethnicity with persistently elevated serum ferritin discovered incidentally and **not** secondary to underlying systemic disease (e.g., chronic alcohol abuse, infection, autoimmunity, malignancy).

Test to Order: Ferritin (hemochromatosis)

For example, an elevated ferritin may be noted as part of an investigation for possible iron deficiency. Such elevations in ferritin should be followed up as patients with hemochromatosis may initially present with non-specific symptoms and upon confirmation of diagnosis would be eligible for therapy.

C. Parents, siblings, and adult children of individuals with **confirmed** genetic diagnosis of *HFE*-HH (i.e., C282Y/C282Y homozygotes).

- Parents: the results of the serum iron tests(s) determine the need for the *HFE* genetic testing (see Appendix A - Figure 2: Laboratory Testing Algorithm)
- Siblings and adult children (≥ 19 years): testing for *HFE* C282Y mutation will proceed in all cases; if C282Y/C282Y homozygote, measure serum ferritin; treat and/or follow as indicated, based on ferritin results.

Test to Order: Ferritin (hemochromatosis). Provide family history on requisition and genetic testing may proceed according to protocol.

Individuals that have previously been treated for hemochromatosis should be offered genetic testing if not already performed. When ordering, indicate that the patient has previously been treated for hemochromatosis.

► **Whom Not to Test**

Screening the general population is not recommended. Testing non-Caucasians for *HFE*-HH is not recommended as the mutation is rare to non-existent in the non-Caucasian population. Non-Caucasian patients with evidence of iron overload should be referred to a specialist

► **Genetic Testing**

Genetic testing is currently only offered through the Molecular Genetics Laboratory (MGL) at the Children's and Women Health Centre of BC.

Genetic testing should **not** be offered to:

- children ≤ 19 years of age**
- non-Caucasians
- first-degree relatives†† of individuals identified to be heterozygous (carriers) for C282Y
- first-degree relatives of individuals previously identified to be compound heterozygotes for C282Y/H63D or to have only the H63D variant

Genetic testing of samples to confirm *HFE*-HH can be done in one of two ways:

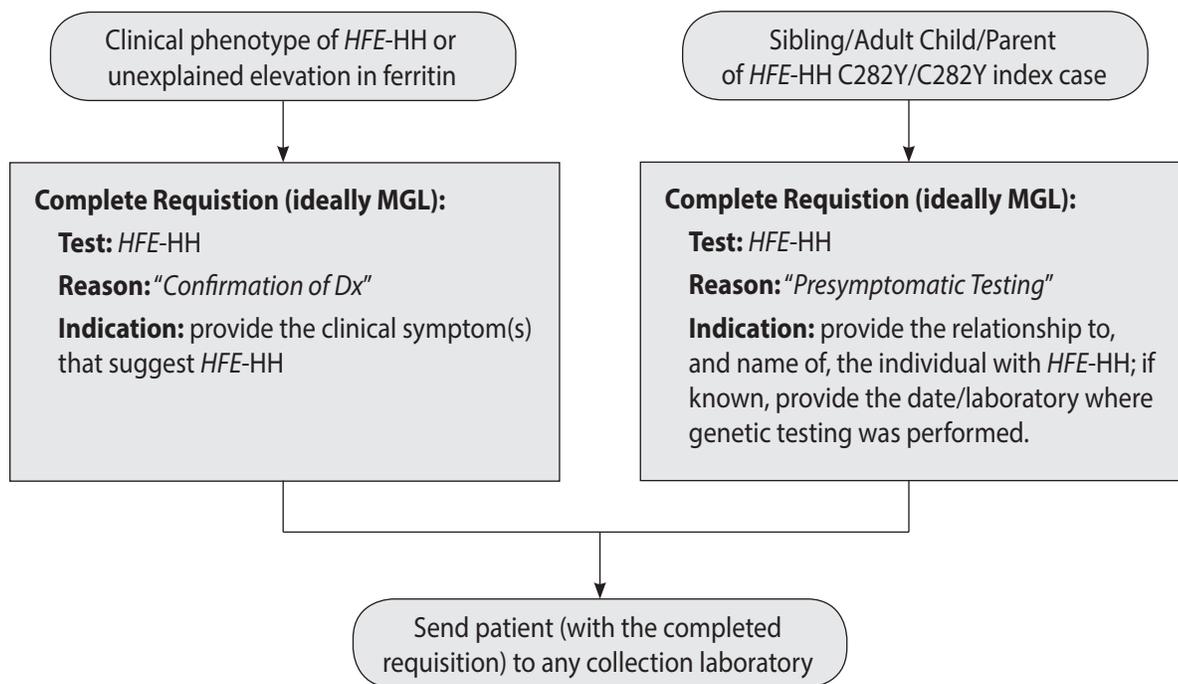
- A. The provincial standard laboratory requisition form (found on the physician secure section of the BCMA website, at www.bcma.org)
 - a. Select *HFE* hemochromatosis testing within the Hematology section (see Appendix A for the testing algorithm followed by laboratories.)
- B. The laboratory requisition from the Molecular Genetics Laboratory (www.genebc.ca)
 - a. Provide reason for testing (check boxes, mid-left side of page) as in Figure 1.

** As *HFE*-HH is an adult-onset disorder, genetic testing is not generally indicated in children <19 years of age. Genetic testing for adult-onset disorders should only be requested when an individual can, themselves, provide informed consent.

†† First-degree relatives: parents, siblings and children.

► Figure 1: Hemochromatosis Test Ordering with MGL Requisition

Note: Requests for ferritin and/or transferrin saturation do NOT constitute requests for *HFE*-HH testing.



Patients in whom iron overload is confirmed in the absence of C282Y/C282Y homozygosity should be referred to a specialist.

Management

► Management and Surveillance of Hemochromatosis

Therapeutic phlebotomy is the treatment of choice for hemochromatosis and for other primary iron overload disorders. Possible exceptions include those who are already anemic, or have limited life expectancy due to other diseases or those with congestive heart failure with hemodynamic instability.

Prior to initiating a phlebotomy program, the patient should be thoroughly assessed for possible end organ damage (e.g., arthritis, liver dysfunction, diabetes, heart disease). Patients with ferritin > 1000 µg/L should have liver function tests because of the increased risk of cirrhosis and hepatoma.^{10,11}

Phlebotomy technique is important for maintaining venous access. Refer to *Appendix B: Therapeutic Phlebotomy Using an 18 Gauge Cannula*.

Volume and frequency of phlebotomy need to be individualized according to the patient's age and clinical and biochemical presentation. For severely iron overloaded patients, weekly phlebotomy of 500 ml of whole blood should be continued until serum ferritin is < 50 µg/L. Patients with massive iron overload may require in excess of 100 phlebotomies.

Serum ferritin and hemoglobin should be monitored regularly (e.g., every 4th phlebotomy) to assess response to therapy. It is unusual for iron overloaded patients to develop anemia early in the course of phlebotomy therapy. If this occurs, the frequency of phlebotomy needs to be reduced.

Once patients have been successfully depleted of excess iron stores (ferritin < 50 µg/L), a program of monitoring and maintenance should be established. The need for maintenance phlebotomy is quite variable; some patients require phlebotomy every 2-4 months to maintain a low-normal ferritin, and some may not re-accumulate for many years.

At minimum, the CBC and ferritin should be checked every 12 months, and phlebotomy should be re-initiated if the ferritin is rising toward the upper limit of normal.

End organ damage should be reassessed periodically. If liver enzymes have been abnormal, they often improve once iron stores have been depleted. There may also be improvement in iron-induced cardiac dysfunction. Diabetic patients often note improvement in blood sugars with less dependency on insulin or oral hypoglycemic agents. Conditions that often do not improve with phlebotomy include arthropathy, cirrhosis and testicular atrophy.

► Notes

- Phlebotomy results in formation of new red cells; therefore HbA1c may underestimate glycemia for up to three months after phlebotomy.
- Although iron can be pharmacologically removed using chelating agents such as deferasirox and desferrioxamine, these are reserved for patients who are unable to tolerate phlebotomy (i.e., patients with chronic anemia due to thalassemia major, myelodysplastic syndromes, etc.). Phlebotomy is safe and cost-effective and thus the preferred modality of iron removal for patients able to tolerate it.
- Strict avoidance of dietary iron is not necessary but iron and vitamin C¹² supplements may need to be avoided. Patients with liver damage should limit or not drink alcohol.¹³
- Patients on maintenance therapy may be eligible to donate to the Canadian Blood Services.

Resources

► References

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- 3 Bacon BR, Adams PC, Kowdley KV, et al. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011;54:328-343.
- 4 Yenson PR, Yoshida EM, Li CH, et al. Hyperferritinemia in the Chinese and Asian community: A retrospective review of the University of British Columbia experience. *Can J Gastroenterol*. 2008;22:37-40.
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- 6 Cook L. Therapeutic phlebotomy - A review of diagnoses and treatment considerations. *J Infus Nurs*. 2010;33:81-88.
- 7 Adams PC, Barton JC. How I treat hemochromatosis. *Blood* 2010;116:317-325.
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- 9 Chen LY, Chang SD, Sreenivasan GM, et al. Dysmetabolic hyperferritinemia is associated with normal transferrin saturation, mild hepatic iron overload, and elevated hepcidin. *Ann Hematol*. 2011;90:139-43.
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- 12 Herbert V. Hemochromatosis and vitamin C. *Ann Intern Med*. 1999;131:475-476.
- 13 Fletcher LM, Dixon JL, Purdie DM, et al. Excess alcohol greatly increases the prevalence of cirrhosis in hereditary hemochromatosis. *Gastroenterology* 2002;122:281-289.

► Diagnostic Codes

257.0 Disorders of iron metabolism

- 275.01 Hereditary hemochromatosis
- 275.02 Hemochromatosis due to repeated red blood cell transfusions
- 275.03 Other hemochromatosis
- 275.09 Other disorders of iron metabolism

► Resources

- Molecular Genetics Laboratory BC www.genebc.ca
- Canadian Hemochromatosis Society: www.cdnhemochromatosis.ca, Toll-Free (Canada): 1 877 BAD-IRON (1 877 223-4766)
- HealthLink BC Dietician Services: www.HealthLinkBC.ca, Dial 811 or TTY (deaf and hearing-impaired) call 711
- Community Healthcare Resource Directory (CHARD) - Information on healthcare specialists and resources www.info.chardbc.ca or Toll Free: 1 877 330-7322

► Appendices

Appendix A - *HFE*-Associated Hemochromatosis Laboratory Testing Algorithm

Appendix B – Therapeutic Phlebotomy Using an 18 Gauge Cannula

This guideline is based on scientific evidence current as of the Effective Date.

This guideline was developed by the Guidelines and Protocols Advisory Committee, approved by the British Columbia Medical Association, and adopted by the Medical Services Commission.

THE GUIDELINES AND PROTOCOLS ADVISORY COMMITTEE

The principles of the Guidelines and Protocols Advisory Committee are to:

- encourage appropriate responses to common medical situations
- recommend actions that are sufficient and efficient, neither excessive nor deficient
- permit exceptions when justified by clinical circumstances

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The Clinical Practice Guidelines (the “Guidelines”) have been developed by the Guidelines and Protocols Advisory Committee on behalf of the Medical Services Commission. The Guidelines are intended to give an understanding of a clinical problem, and outline one or more preferred approaches to the investigation and management of the problem. The Guidelines are not intended as a substitute for the advice or professional judgment of a health care professional, nor are they intended to be the only approach to the management of clinical problem.

We cannot respond to patients or patient advocates requesting advice on issues related to medical conditions. If you need medical advice, please contact a health care professional.

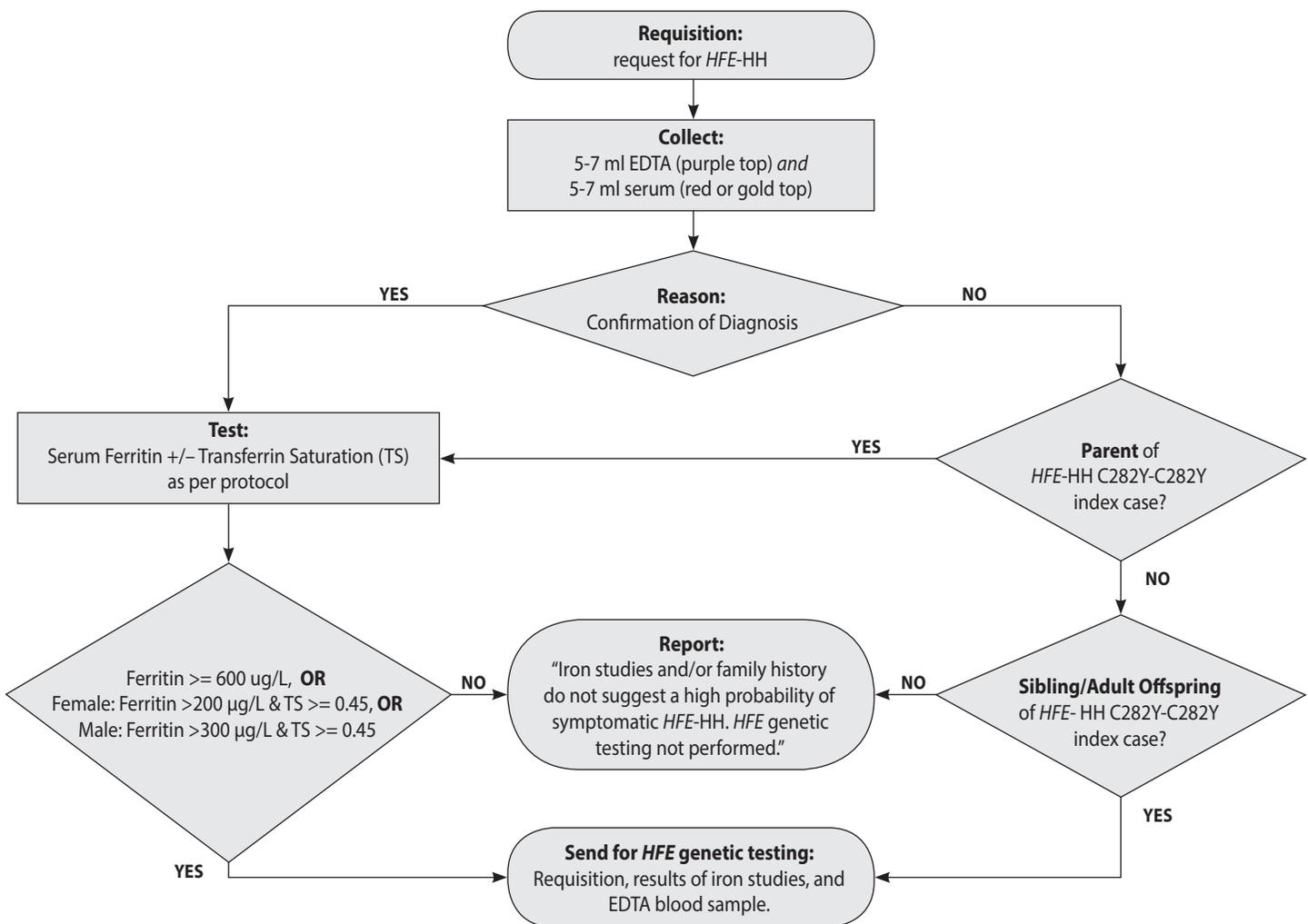


Appendix A: HFE-Associated Hemochromatosis Laboratory Testing Algorithm

In all cases, the laboratory will collect a serum sample for serum iron studies (serum ferritin, serum transferrin, TIBC) and an EDTA sample for *HFE* C282Y genetic testing.

- A. For those presenting with symptoms and signs of hemochromatosis, or with persistently elevated ferritin levels, the results of the serum iron studies will determine whether or not genetic testing will be done (see Figure 2).
- B. First-degree relatives of individuals with confirmed hemochromatosis due to C282Y homozygosity (i.e., genotype C282Y/C282Y) may or may not have iron studies performed prior to genetic testing (see Figure 2).

► **Figure 2: Laboratory Testing Algorithm**





Appendix B: Therapeutic Phlebotomy Using an 18 Gauge Cannula

The standard equipment provided for phlebotomy is a blood collection unit with a 15 gauge stainless steel needle attached to the unit. The large inflexible needle makes venipuncture difficult if the patient has poor or limited venous access.

The equipment and procedure used here are effective and yet:

- provide more choice of venous access
- patients report the procedure is more comfortable as the cannula is smaller and softer
- patients and nurses report less bleeding post cannula removal.

Equipment

1. 18 ga x 11/4 inch teflon coated IV catheter
2. extension set, luer lock adapters, 38 cm
3. injection cap, 7/8 inch, male luer lock
4. single blood pack unit without anticoagulant
5. BP cuff
6. alcohol swabs
7. sterile 2 x 2 inch gauze
8. tape
9. clamps x 2
10. weigh scale
11. stretcher with adjustable height
12. clean gloves

Procedure

A. Prepare patient

1. provide explanation
2. lay patient down
3. baseline BP and pulse
4. apply heat to arms prn
5. provide a handgrip prn
6. sedation as ordered

B. Prepare equipment

1. open extension set, close clamp
2. attach injection cap to female end of extension unit
3. clean injection cap with alcohol swab
4. insert needle of blood collection unit into injection cap

C. Perform venipuncture

1. BP cuff to 90 mm Hg, clamp to prevent leakage
2. select and clean site
3. glove
4. perform venipuncture, advance cannula to hub
5. attach male adapter to IV device
6. release pressure
7. secure cannula: tape extension set to arm; gauze over venipuncture site

D. Perform phlebotomy

1. open clamp on extension set
2. apply pressure by pumping BP cuff to 60 mm Hg
3. lower collection unit to scale to measure volume
4. adjust flow by the height of bed and pressure of cuff
5. on completion, release BP cuff, clamp extension set, and remove IV device
6. apply pressure, dress site
7. monitor patient and discharge per protocol