BCGuidelines.ca
Guidelines & Protocols Advisory Committee

High Ferritin and Iron Overload – Investigation and Management

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Scope

This guideline is directed to primary care practitioners who encounter an unexplained finding of high ferritin in an adult outpatient aged >19 years. It provides recommendations for the investigation of high ferritin levels (hyperferritinemia), outlines common causes of hyperferritinemia and gives practitioners guidance on when to investigate for and treat hereditary hemochromatosis.

The guideline is not for screening for iron overload.

Hemochromatosis caused by mutations in iron-related genes other than *HFE* is outside the scope of this guideline. *HFE* (high Fe) is the gene most commonly associated with hemochromatosis. Because the non-*HFE* hereditary hemochromatosis causes of hyperferritinemia are so diverse, their management is out of scope. They should be managed according to the underlying condition.

Key Recommendations*

- Ferritin is an acute phase reactant released by activated macrophages and damaged hepatocytes.
- High ferritin levels are most commonly caused by inflammation, infection, liver disease (particularly non-alcoholic steatohepatitis (NASH)/fatty liver), renal disease, alcohol excess, metabolic syndrome or malignancy. In these cases, a high ferritin level does not accurately reflect iron stores.[1]
- The first-line investigations for a patient with a raised serum ferritin are:
  - **History taking:** alcohol intake and other risk factors for liver disease, type 2 diabetes mellitus, obesity, hypertension, signs and symptoms of an underlying inflammatory or malignant disorder, transfusion history, and family history of iron overload.
  - **Lab tests:** repeat serum ferritin, transferrin saturation (TSAT), complete blood count, serum creatinine, liver enzymes (ALT and GGT) with consideration of viral hepatitis screening and abdominal ultrasonography (if suspected liver disease or elevated liver enzymes). Check blood glucose and lipid studies if not recently performed.
- Hereditary hemochromatosis is an uncommon cause of hyperferritinemia and testing for *HFE*-HH is not recommended in patients of non-European ancestry because its prevalence is very rare.
- Individuals of East Asian descent have ferritin values 1.5-2x higher than the upper limit of normal reported.
- Iron overload can generally be excluded when TSAT <45%.

* The key recommendations are adapted from the 2018 British Journal of Hematology Guideline *Investigation and management of a raised serum ferritin*[1] and modified to fit the BC primary care context.

Definitions and Clinical Context

Hyperferritinemia: occurs when a patient's serum ferritin is above the upper reference interval. The upper reference interval varies with age, gender, and laboratory method. Individuals of East Asian descent have ferritin values 1.5-2x higher than the reference norms reported.[2] Refer to Appendix A: Suggested laboratory thresholds for addition of an abnormal result flag and addition of interpretive comments on ferritin testing. High ferritin alone does not indicate iron overload.

Iron overload: occurs when iron absorption exceeds physiological requirements, leading to excess stores because there is a limited physiological capacity (i.e., blood loss) to get rid of excess iron. This is indicated by TSAT ≥45% and can occur from:

- Transfusion-dependent anemias (e.g., myelodysplastic syndromes (MDS), sickle cell anemia)
- Anemia from ineffective erythropoiesis (e.g., thalassemia, MDS)
- Chronic excessive ingestion of medicinal iron
- Hereditary hemochromatosis (HH)

***HFE*-associated Hereditary Hemochromatosis (*HFE*-HH):** is an autosomal recessive genetic disorder common in individuals of European ancestry, in which an increase in the intestinal absorption of iron leads to excessive iron deposits in organs such as liver, pancreas, heart, pituitary, testicles, joints, and skin. Early detection and treatment can completely prevent clinical sequelae, and, in symptomatic patients, phlebotomy effectively reduces morbidity and mortality.[3,4]

HFE-HH has a relatively low clinical penetrance, with fewer than 10% of those homozygous for the C282Y variant (the most common mutation) developing clinical manifestations, which usually present by age 40-50 in men and age 50-60 in women (Appendix B: Nonspecific signs and symptoms of extreme iron overload by organ).[5] Liver impairment is the most common presentation. Nonspecific symptoms such as arthralgias, fatigue, and abdominal pain may be noted years before organ dysfunction becomes apparent. If untreated, iron overload can cause serious organ damage and premature death but end-organ damage is rare with a ferritin value < 600 µg/L.

Over 80% of *HFE*-HH is due to homozygous mutation for C282Y in the *HFE* gene.[3,4] Hemochromatosis caused by mutations in other iron-related genes are rare and are outside the scope of this guideline.[6] Suspected cases should be referred to a specialist. Information on the epidemiology of *HFE*-HH is provided in Appendix C: Epidemiology of *HFE* hemochromatosis.

Signs and Symptoms

Signs and symptoms of high ferritin levels

The signs and symptoms of high ferritin are due to the underlying conditions (e.g., infection) and not due to the high ferritin in and of itself.

Signs and symptoms of iron overload

Iron overload is often missed because its symptoms are nonspecific and gradual multiorgan damage occurs over many years. Its symptoms can mimic those of much more common diseases, such as alcoholic liver disease, diabetes, and osteoarthritis.

Nonspecific symptoms of extreme iron overload are provided in Appendix B: Nonspecific signs and symptoms of extreme iron overload by organ. Iron overload does not cause a high hemoglobin.

Diagnosis

Differential diagnosis of high ferritin

This may include inflammatory disorders, liver disease (particularly non-alcoholic steatohepatitis (NASH)/fatty liver), alcohol excess, malignancy, renal failure, and metabolic syndrome, which are each more common than hemochromatosis.[1] Fatty liver is a very common cause of high ferritin in outpatients.[7–9]

Extreme hyperferritinemia >3000 µg/L can be seen in transfusional iron overload, severe liver disease, hemophagocytic syndromes, renal failure, sepsis, severe inflammation and other severe illnesses, typically in a hospital setting.

In patients with serum ferritin levels >10,000 µg/L, acute hepatitis and rare conditions such as adult onset Still disease, hemophagocytic lymphohistiocytosis and hematological malignancies should be considered.

Table 1. Causes of raised serum ferritin (adapted from Table 1, Cullis 2018[1])

Not associated with significant iron accumulation	As a result of cellular damage	Due to iron accumulation
• Acute and chronic infection • Chronic inflammatory disorders • Autoimmune disorders • Malignancies • Malignant or reactive histiocytosis • Hereditary hyperferritinemia with and without cataracts • Gaucher disease	• Chronic excess alcohol consumption • Liver diseases including: liver failure, chronic viral hepatitis, alcoholic and non-alcoholic steatohepatitis[†]	• Hereditary hemochromatosis • Secondary iron overload from blood transfusion or excessive iron intake/ administration • Ineffective erythropoiesis: sideroblastic anemia, some myelodysplastic syndromes (e.g., refractory anemia with ring sideroblasts) • Thalassemia • Other rare genetic disorders

History taking

Key questions to ask in a patient with raised serum ferritin levels:

1. Extent of alcohol intake
2. Risk factors for viral hepatitis (e.g., travel, high risk activities such as intravenous drug use)
3. Signs and symptoms or known inflammatory condition (e.g., rheumatoid arthritis)
4. Signs and symptoms or known malignancy
5. Diabetes mellitus and risk factors
6. Metabolic syndrome (hypertension, diabetes, obesity)
7. History of blood transfusions, specifically, frequency and duration of red cell or whole blood transfusion
8. Family history of iron overload, hemochromatosis, anemia, hemoglobinopathies or other hematological conditions

[†] May also have iron overloading.

Initial laboratory investigations

- If the serum ferritin is elevated and there is a potential transient cause (e.g., acute infection, flare of a chronic inflammatory condition), recheck the serum ferritin no earlier than one week after the transient cause has resolved.
- Unless recently investigated, the following tests are recommended for patients with an unexplained, persistently elevated serum ferritin level:
  - TSAT (fasting sample not required)
  - CBC
  - high sensitivity C-reactive protein (only if indicated according to BC Guidelines: C-Reactive Protein and Erythrocyte Sedimentation Rate Testing)
  - serum creatinine
  - ALT and GGT: if elevated, investigate for common causes of hepatitis (e.g., viral, NASH, alcohol)
  - abdominal ultrasound if clinical suspicion for liver disease or liver enzymes are elevated
  - glucose and HbA1C
  - lipid studies
- If TSAT <45%, then iron overload is generally excluded and no follow-up is required. For borderline unexplained levels, there is no urgency to re-check TSAT before 6 months.
- If TSAT ≥45%, then investigations for causes of iron overload is indicated, unless obvious causes are apparent such as multiple transfusions (see Table 1 and Definition and Clinical Context – Iron Overload).

Investigations to determine degree of iron overload

In some cases, patients may need additional testing to confirm or rule out iron overload, which may include MRI of the heart or liver. This is arranged by a specialist and the specific MRI protocols to assess for iron are not widely available.

Testing for *HFE*-HH

Indications for genetic testing

Genetic testing for *HFE*-HH is indicated in patients of European descent with a persistently elevated serum ferritin AND TSAT ≥45%. The tests that the laboratory will perform for each indication are described in Appendix E: Laboratory Test Procedures for *HFE*-HH Testing, The patient can go to any collection laboratory. Identification of HH through genetic testing will eliminate the need for liver biopsy in those with TSAT ≥45% and provides diagnosis confirmation prior to initiation of phlebotomy.

HFE-HH testing is not recommended for individuals of East and South Asian descent, or those of other non-European ancestries, because HFE-HH is extremely rare in these groups. Further information on non-indications for testing *HFE*-HH is provided in Appendix D: Scenarios in which genetic testing for *HFE*-HH is not indicated.

Patients previously treated for *HFE*-HH where the genetic test result is unavailable

Individuals who have previously been treated for *HFE*-HH should be offered genetic testing if not already performed. For ordering guidance, see BCCH/BCWH Division of Genome Diagnostics webpage (www.genebc.ca) under frequently asked questions.

Completing the standard outpatient laboratory requisition

The following table outlines the appropriate settings for testing for *HFE*-HH and how to fill out the laboratory requisition. **Checking the specific categories in the laboratory requisition facilitates appropriate genetic testing.**

Table 2. Indications for *HFE*-HH testing and instructions for filling out the laboratory requisition

Indication for *HFE*-HH Genetic Testing	How to fill out the standard out-patient laboratory requisition[‡]
Testing for patients with clinical features of iron overload	
Individuals of European ancestry with raised ferritin and TSAT ≥45%	Under HFE-Hemochromatosis, check off "Confirm diagnosis"
Cascade testing for a patient with family history of hemochromatosis	
Patient has a child with C282Y;C282Y *HFE* genotype	Under HFE-Hemochromatosis, check off "Confirm diagnosis"
Adult patient with family history of hemochromatosis (genotype of relative is unknown or not *HFE* C282Y;C282Y)	
Adult patient's sibling or parent has confirmed C282Y;C282Y *HFE* genotype	Under HFE-Hemochromatosis, check off "Sibling/parent is C282Y/C282Y homozygote"
Patient < 19 years old with family history of hemochromatosis	See Appendix D: Scenarios in which genetic testing for *HFE*-HH is not indicated

Interpreting Results from HFE-HH Testing

Genetic counselling

Genetic counselling, patient education, and testing of first-degree relatives should be performed by the primary care practitioner. Refer to Frequently Asked Questions at genebc.ca for more information. Most genetics clinics do not accept referrals for *HFE*-HH genetic counselling.

Patients homozygous for *HFE* C282Y (C282Y;C282Y)

Patients with hyperferritinemia, TSAT > 45% and genetic testing confirming C282Y homozygosity have a diagnosis of *HFE*-HH. Most will require reduction of their iron stores with a phlebotomy program (can be supplemented by regular blood donation) (see Appendix F: Management and surveillance of *HFE*-HH). Good phlebotomy technique is important for maintaining venous access long term (see Appendix G: Therapeutic Phlebotomy Using an 18 Gauge Cannula). 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 > 1,000 µg/L should have liver function tests because of the increased risk of cirrhosis and hepatoma.[10] Management and surveillance of patients with a diagnosis of *HFE*-HH are provided in Appendix F: Management and surveillance of *HFE*-HH.

Patients heterozygous for *HFE* C282Y

Patients heterozygous for HFE C282Y are most often asymptomatic carriers. However, they may have a clinical phenotype of HH due to co-inheritance of other genetic factors (e.g., another mutation such as H63D in the same gene, or a co-inherited mutation in another gene), and/or other comorbidities (e.g., alcohol use disorder, hepatitis C).[8] If the clinical phenotype strongly suggests HH, refer to a specialist to consider hepatic iron studies and/or need for additional genetic investigations. In majority of these cases, genetic testing will not affect clinical management.

[‡] The standard out-patient laboratory requisition (SOPLR) is available from: gov.bc.ca/assets/gov/health/forms/1901fil.pdf

Indications for Specialist Referral

The following patients should be referred to a specialist (i.e., general internist, gastroenterologist/hepatologist or hematologist) for further investigations or management:

- *HFE*-HH with organ dysfunction or damage (e.g., cirrhosis, heart failure)
- Absence of C282Y;C282Y homozygosity, including heterozygous for *HFE* C282Y, with serum ferritin > 1,000 µg/L and TSAT ≥45% or clinical features of iron overload
- **Unexplained** persistent serum ferritin > 1,000 µg/L, with or without clinical or laboratory evidence of iron overload (see Table 1)

Recommended history and tests to include in referral package

History containing clinical features suggestive of iron overload and results from first line investigations indicated above. Genetic studies and family history should be included if available.

Please use for referral:

- Use Pathways to see the list of specialists in your region and their wait times.
- Real-time communication with local specialists (or RACE Line if uncertain) can provide rapid advice for urgent cases and facilitate the most appropriate mechanism of referral.

Resources

Practitioner Resources

- BC Children's Hospital and BC Women's Hospital (BCCH/BCWH) Department of Pathology and Laboratory Medicine, Division of Genome Diagnostics: genebc.ca
  - Refer to Frequently Asked Questions

Patient, Family and Caregiver Resources

- HealthLink BC: healthlinkbc.ca/health-topics/hw180388
- Canadian Hemochromatosis Society: toomuchiron.ca
- Canadian Blood Services – Information about blood donation for individuals with hemochromatosis: blood.ca/en/blood/am-i-eligible/abcs-eligibility/hemochromatosis

How this guideline was developed

This guideline was adapted from the British Journal of Hematology Guideline *Investigation and management of a raised serum ferritin*[1] to fit the BC primary care context. The working group included representatives of family medicine, hematology, gastroenterology, radiology, medical biochemistry and molecular genetics. We added guidance on diagnosis and management of hereditary hemochromatosis, based on the BC Guideline *HFE-Associated Hemochromatosis Investigations and Management* (2013).

For more information about how BC Guidelines are developed, please refer to the GPAC Handbook.

References

1. Cullis JO, Fitzsimons EJ, Griffiths WJ, Tsochatzis E, Thomas DW. Investigation and management of a raised serum ferritin. Br J Haematol. 2018;181(3):331–40.
2. Tahmasebi H, Asgari S, Hall A, Higgins V, Chowdhury A, Thompson R, et al. Influence of ethnicity on biochemical markers of health and disease in the CALIPER cohort of healthy children and adolescents. Clin Chem Lab Med. 2020 Mar 26;58(4):605–17.
3. Adams PC, Reboussin DM, Barton JC, McLaren CE, Eckfeldt JH, McLaren GD, et al. Hemochromatosis and iron-overload screening in a racially diverse population. N Engl J Med. 2005 Apr 28;352(17):1769–78.
4. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS, American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatol Baltim Md. 2011 Jul;54(1):328–43.
5. Waalen J, Felitti VJ, Gelbart T, Beutler E. Screening for hemochromatosis by measuring ferritin levels: a more effective approach. Blood. 2008 Apr 1;111(7):3373–6.
6. Lok CY, Merryweather-Clarke AT, Viprakasit V, Chinthammitr Y, Srichairatanakool S, Limwongse C, et al. Iron overload in the Asian community. Blood. 2009 Jul 2;114(1):20–5.
7. Mörwald K, Aigner E, Bergsten P, Brunner SM, Forslund A, Kullberg J, et al. Serum Ferritin Correlates With Liver Fat in Male Adolescents With Obesity. Front Endocrinol. 2020;11:340.
8. Kowdley KV, Belt P, Wilson LA, Yeh MM, Neuschwander-Tetri BA, Chalasani N, et al. Serum ferritin is an independent predictor of histologic severity and advanced fibrosis in patients with nonalcoholic fatty liver disease. Hepatol Baltim Md. 2012 Jan;55(1):77–85.
9. Fargion S, Mattioli M, Fracanzani AL, Sampietro M, Tavazzi D, Fociani P, et al. Hyperferritinemia, iron overload, and multiple metabolic alterations identify patients at risk for nonalcoholic steatohepatitis. Am J Gastroenterol. 2001 Aug;96(8):2448–55.
10. Guyader D, Jacquelinet C, Moirand R, Turlin B, Mendler MH, Chaperon J, et al. Noninvasive prediction of fibrosis in C282Y homozygous hemochromatosis. Gastroenterology. 1998 Oct;115(4):929–36.
11. Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q, et al. The mutational constraint spectrum quantified from variation in 141,456 humans. Nature. 2020;581(7809):434–43.
12. Karczewski KJ, Francioli LC, Tiao G, Cummings BB, Alföldi J, Wang Q, et al. The mutational constraint spectrum quantified from variation in 141,456 humans [Internet]. Genomics; 2019 Jan [cited 2020 Jun 5]. Available from: http://biorxiv.org/lookup/doi/10.1101/531210
13. Government of Canada SC. Focus on Geography Series, 2016 Census - Province of British Columbia [Internet]. 2017 [cited 2020 Sep 3]. Available from: https://www12.statcan.gc.ca/census-recensement/2016/as-sa/fogs-spg/Facts-PR-Eng.cfm?TOPIC=7&LANG=Eng&GK=PR&GC=59
14. Guidelines for genetic testing of healthy children. Paediatr Child Health. 2003 Jan;8(1):42–5.
15. Delatycki M, Wolthuizen M, Collins V, Varley E, Craven J, Allen K, et al. Implementation of ironXS: a study of the acceptability and feasibility of genetic screening for hereditary hemochromatosis in high schools. Clin Genet. 2010 Mar;77(3):241–8.
16. Delatycki M, Wolthuizen M, Aitken M, Hickerton C, Metcalfe S, Allen K. To tell or not to tell - what to do about p.C282Y heterozygotes identified by HFE screening: Should HFE p.C282Y heterozygotes be told their genotype? Clin Genet. 2013 Sep;84(3):286–9.
17. Herbert V. Hemochromatosis and vitamin C. Ann Intern Med. 1999 Sep 21;131(6):475–6.

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

Abbreviations

***HFE*-HH**	*HFE*-associated hereditary hemochromatosis. *HFE* (high Fe) is the gene most commonly associated with hemochromatosis
NASH	non-alcoholic steatohepatitis
TSAT	transferrin saturation

Appendices

Appendix A: Suggested laboratory thresholds for addition of an abnormal result flag and addition of interpretive comments on ferritin testing

Appendix B: Nonspecific signs and symptoms of extreme iron overload by organ

Appendix C: Epidemiology of HFE hemochromatosis

Appendix D: Scenarios in which genetic testing for *HFE*-HH is not indicated

Appendix E: Laboratory Test Procedures for *HFE*-HH Testing

Appendix F: Management and surveillance of *HFE*-HH

Appendix G: Therapeutic Phlebotomy Using an 18 Gauge Cannula

Associated Documents

BC Guideline: Iron Deficiency – Investigation and Management

BC Guideline Ultrasound Prioritization

BC Guideline: C-Reactive Protein and Erythrocyte Sedimentation Rate Testing

BC Guideline: Viral Hepatitis Testing

This guideline is based on scientific evidence current as of the effective date.

This guideline was developed by the Guidelines and Protocols Advisory Committee in collaboration with the Provincial Laboratory Medicine Services, and adopted under the Medical Services Act and the Laboratory Services Act.

For more information about how BC Guidelines are developed, refer to the GPAC Handbook available at BCGuidelines.ca: GPAC Handbook.

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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Appendix A: Suggested laboratory thresholds for addition of an abnormal result flag and addition of interpretive comments on ferritin testing

Elevated ferritin result (µg/L)	Suggested Laboratory reporting comment
200 - <400	Ferritin results under 400 µg/L generally do not require further investigation.
400 – 600*	Mild elevations in ferritin are most frequently an acute phase reaction.
>600*	Significant elevations in ferritin may indicate iron overload.

Results above 400 µg/L will be flagged as an abnormal result in the laboratory report. There is variability between laboratory ferritin methods and so the abnormal flag is applied non-uniformly across laboratories in BC. The 200, 400 and 600 µg/L cutpoints are guide posts rather than strict delimiters of the need for further follow-up.

Note: Individuals of East Asian descent have ferritin values 1.5-2x higher than the upper limit of normal reported.

Appendix B: Nonspecific signs and symptoms of extreme iron overload by organ

In a patient with a high ferritin result, the presence of multiple signs or symptoms listed here may indicate underlying iron overload.

Iron Storage	Consequences
Liver (common)	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 or atypical presentation (e.g., young, low BMI)
Skin	Increased skin pigmentation ("bronze"); association with porphyria cutanea tarda
Hair	Body 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

Appendix C: Epidemiology of HFE hemochromatosis

HFE-HH is the most common genetic disorder in the western world. Approximately 1 in 300 individuals of European ancestry are homozygous for the C282Y *HFE* gene variant[11] (i.e., both copies of the *HFE* gene carry this genetic change) and 1 in 9 such individuals are carriers (see Table 2). *HFE*-HH is rare in individuals of other ancestries, including individuals of East Asian or South Asian descent, largely due to the rarity of the C282Y variant in these non-European populations.[12]

Table 1. Estimated number of people with *HFE* C282Y in the BC population based on the Canadian 2016 Census[13]

Genotype	Estimated # individuals in BC
Homozygote (C282Y;C282Y)	7846
Heterozygote	362,622

Table 2. *HFE*-HH-C282Y in different populations[11]

Population	Homozygote frequency (%)	Carrier frequency (%)
European	0.33	11.0
Latino	0.02	2.7
African	0.01	2.1
South Asian	~0	0.4
East Asian	~0	0.03

Appendix D: Scenarios in which genetic testing for *HFE*-HH is not indicated

The following scenarios do not warrant genetic testing for *HFE*-HH:

- Screening the general population.
- Testing individuals of non-European descent for *HFE*-HH as the C282Y variant is exceedingly rare in the non-European population; thus, a negative *HFE*-HH genetic test has no clinical utility. See Appendix C: Epidemiology of HFE hemochromatosis for the prevalence of hereditary hemochromatosis in different populations. Non-European patients with evidence of iron overload (persistently high ferritin AND TSAT ≥45%) should be referred to a specialist.
- Patients with clinical findings (see Appendix B: Nonspecific signs and symptoms of extreme iron overload by organ) that are found in iron overload but who do not have a TSAT ≥45%.
- As *HFE*-HH is an adult-onset disorder, genetic testing is not generally indicated in children and so can be deferred until the child is able to exercise autonomy regarding decision making.[14,15]
- Parents of individuals homozygous for C282Y (i.e., C282Y;C282Y genotype) who do not themselves have hyperferritinemia and a TSAT ≥45%.
- First-degree relatives (parents, siblings and children) of individuals identified to be heterozygous for C282Y (whether C282Y/wild type or C282Y/H63D) who do not have hyperferritinemia and a TSAT ≥45%.
- First-degree relatives (parents, siblings and children) of individuals with non-C282Y *HFE* genotypes who do not themselves have hyperferritinemia and a TSAT ≥45%.[16]

Appendix E: Laboratory Test Procedures for *HFE*-HH Testing

This Appendix outlines the testing the laboratory will perform based on the requisition. Refer to Table 2 for the indications for testing and associated instructions for filling out the requisition.

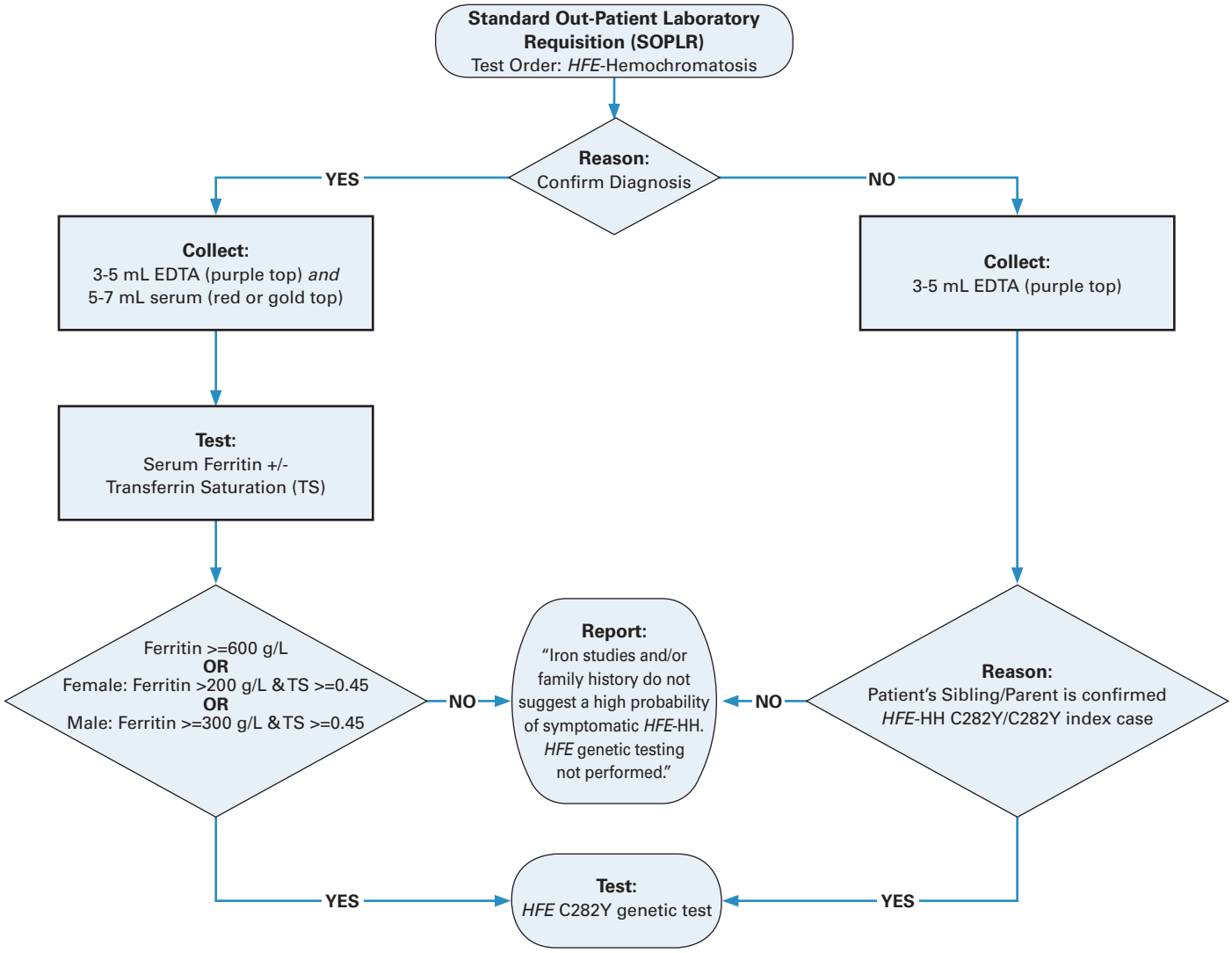
In all cases, the laboratory will collect an EDTA sample for *HFE* C282Y genetic testing and, where applicable, a serum sample for serum iron studies (serum ferritin, serum transferrin, TIBC).

A. For those presenting with signs and symptoms of hemochromatosis, or with persistently elevated ferritin levels, or with a family history of hemochromatosis (genotype of relative unknown or not C282Y;C282Y) , the results of the serum iron studies will determine whether or not genetic testing will be done (see Figure 1 below).

B. Siblings and children of individuals with confirmed *HFE*-HH due to C282Y homozygosity (i.e., genotype C282Y; C282Y) will not have iron studies performed prior to genetic testing (see Figure 1).

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

Figure 1: Hemochromatosis Test Procedure



Appendix F: Management and surveillance of *HFE*-HH

Therapeutic Phlebotomy

- Phlebotomy is the treatment of choice for HH 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.
- Volume and frequency of phlebotomy need to be individualized according to the patient's age and clinical and biochemical presentation. Some patients will tolerate weekly phlebotomy but most will not tolerate phlebotomy more frequently than every 2 – 4 weeks and smaller volumes may be indicated in women. Guidelines recommend that for severely iron overloaded patients, weekly phlebotomy of 500 ml of whole blood should be continued until serum ferritin is 50-100 µg/L, within the patient's tolerance. Consider venous access, frequency of phlebotomy, and symptoms of iron deficiency). 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, reduce the frequency of phlebotomy.
- 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, ferritin and TSAT should be checked every 12 months, and phlebotomy should be re-initiated if the ferritin or TSAT is rising toward the upper limit of normal.
- People with hemochromatosis can donate blood, provided they meet all other Canadian Blood Services donor eligibility criteria. See details from Canadian Blood Services at: blood.ca/en/blood/am-i-eligible/abcs-eligibility/hemochromatosis

Chelation

- Patients with *HFE*-HH respond to phlebotomy and do not require chelating agents such as deferasirox and desferrioxamine.

Organ Damage

- In patients with organ damage, such as cirrhosis, congestive heart failure, hypogonadism, referral to the relevant specialist is recommended.
- End organ damage should be reassessed periodically. Reversal of organ impairment is sometimes seen once iron stores have been depleted. For example, if liver enzymes have been abnormal, they often improve with phlebotomy. 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.

Dietary Restriction

- Strict avoidance of dietary iron is not necessary, but iron and vitamin C supplements should be avoided.[17] Patients can access the support of a dietitian through HealthLink BC.

Appendix G: 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 overvenipuncture 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