

OBJECTIVE

Alberta clinicians are assisted to

- Diagnose patients at risk for HFE gene-associated hemochromatosis
- Prevent end-organ disease by early diagnosis
- Optimize clinical investigations followed by genetic testing
- Counsel and manage patients with a definitive diagnosis

TARGET POPULATION

Adults 18 years and older

EXCLUSIONS

Population screening for hereditary hemochromatosis

Children under 18 years of age

Note: The recommendations in this clinical practice guideline are based on the collective understanding of the evidence available at this time, the different approaches used in other jurisdictions, and clinical expertise and experience in Alberta

RECOMMENDATIONS

SCREENING

- ✓ Consider patients* for screening if they have:
 - Unexplained bronze or gray skin discoloration
 - End-organ disease
 - Family history of confirmed hemochromatosis (see [Algorithm](#))
- * Hemochromatosis is more common in people of Northern European heritage
- ✓ Screen using percent iron saturation and ferritin, in the fasting state, on one occasion if suspicion is low. If suspicion is high, screen twice to confirm.
- ✓ Suspect genetic hemochromatosis if iron saturation > 45%, particularly if ferritin is > 300 ng/mL in males or 200 ng/mL in females
- X DO NOT measure ferritin alone. Ferritin is NOT an adequate measure since it is an acute phase reactant which can be elevated in acute and chronic infection, inflammation and neoplasm

GENETIC TESTING

- ✓ Perform the genetic test if screening is suggestive of genetic hemochromatosis. The genetic test determines mutations in the HFE gene – C282Y and H63D (or S65C).

- ✓ Use the Molecular Diagnostic laboratory requisition for Edmonton or Calgary to order the test
- ✓ Provide basic genetic information to the lab prior to ordering genetic testing
- ✓ Consider the potential for insurance discrimination for asymptomatic patients
- ✓ Refer to Medical Genetics Clinics in Edmonton or Calgary if further counselling is necessary

MANAGEMENT

- ✓ Ferritin should be lowered to:
 - 50-100ng/mL in patients with evidence of end-organ damage
 - < 200ng/mL in women without evidence of end-organ damage
 - < 300 ng/mL in men without evidence of end-organ damage
- ✓ Maintain hemoglobin above 110 g/L
- ✓ Encourage regular blood donation if the patient is a suitable blood donor. Hemochromatosis is NOT transmissible through a blood donation.

THIS GUIDELINE DOES NOT:

- X Address rare forms of genetic hemochromatosis that are associated with other genes such as juvenile hemochromatosis, and environmentally induced hemochromatosis
- X Recommend universal screening for hereditary hemochromatosis. It is not yet clear which proportion of the population with genetic risk or biochemical evidence of iron overload will develop the clinical complications of iron overload.

Refer to [Algorithm](#) for Screening and Management for Clinical Suspicion of HFE Hemochromatosis

BACKGROUND

DESCRIPTION OF THE PROBLEM

Hemochromatosis is a disorder of excessive iron stores. Iron may be acquired in many ways and, once in the body, must be stored. Iron is toxic to some tissues and causes end-organ damage:

- Liver – cirrhosis and the potential for hepatocellular carcinoma if cirrhosis diagnosed
- Heart – congestive heart failure
- Pancreas – diabetes (loss of Islet cells)
- Joints – arthritis
- Skin – abnormal pigmentation (bronze or grey)
- Pituitary – hypothyroidism, hypogonadism
- Testis – impotence¹

ACQUIRING HEMOCHROMATOSIS

GENETIC MEANS:

Genetic hemochromatosis, associated with mutations in the HFE gene, is the most common inherited disorder among Caucasian populations, and typically affects individuals of north European descent.^{2,3} The prevalence of the disorder is reported to be between one in 200 and one in 400 in western countries.³ Rare forms of genetic hemochromatosis, including neonatal and juvenile hemochromatosis, are associated with other genes. As well, there are genetic forms of hemochromatosis which are known to exist, but the genetic cause is not yet elucidated.

ENVIRONMENTAL MEANS:

Individuals with chronic anemia (whether genetic such as congenital hemolytic anemia or acquired from bone marrow failure), who require frequent transfusions, can also develop iron overload. Rarely, exogenous iron in the diet can cause iron overload such as with the African Bantus who acquire large amounts of iron through brewing beer in iron pots.⁴ Individuals with chronic liver disease can also accumulate large stores of iron in the liver independent of any genetic predisposition.

INHERITING HFE HEMOCHROMATOSIS

The HFE gene is located on chromosome 6 and was cloned in 1996.⁵ The gene product controls the rate of absorption of iron from the small bowel. There are three common alleles – normal, C282Y and H63D. There is also a rare mutation called S65C which is clinically identical to H63D. C282Y is almost exclusively found in populations of northern European heritage. H63D is less common and distributed fairly equally around the world.

Individuals must have two abnormal alleles to be at significantly increased risk for symptomatic hemochromatosis. Hence, hemochromatosis is an autosomal recessively inherited disorder. Those who have the genetic constitution C282Y/C282Y have an approximately 70% chance of developing excess iron levels, but only approximately 10-30% develop end-organ symptoms. Those who have the genetic constitution C282Y/H63D have only a few percent chance of developing symptomatic disease. Homozygotes for H63D/H63D almost never develop significant iron overload. The heterozygotes, N/C282Y and N/H63D are not at increased risk for symptomatic iron overload.^{1,5}

For individuals of northern European heritage, approximately three to four of 1000 will have a genetic constitution which confers significant risk for iron overload disease. Another 10-15% will be heterozygotes (carriers).⁵ Even though this is a recessive disorder, the high frequency of the abnormal alleles in this population can result in a family history of affected individuals in more than one generation.

SYMPTOMATIC DISEASE

Iron overload does not always occur even amongst individuals born with a genetic predisposition to absorb and store excess iron i.e., those with the genetic constitution C282Y/C282Y or C282Y/H63D. This is partially due to the alleles themselves – C282Y being much more severe in effect than H63D.^{1,5}

Environmental factors, however, are also very important. Development of iron stores requires time; therefore dangerous amounts do not accumulate until well into adulthood. Women accumulate iron

slower than men due to periodic loss of iron through menses and childbearing. Vegetarians acquire less iron through food than heavy meat eaters. Iron supplements, a component in the majority of multivitamin preparations, may add to iron stores while regular blood donations deplete stores. There are additional genetic and acquired factors which can influence end-organ damage.⁶ Coincidental insults to the liver such as excessive alcohol use or chronic viral hepatitis can accelerate the onset of liver damage in an individual with a genetic predisposition to hemochromatosis

Typically, the clinical manifestations of hereditary hemochromatosis present around 30 to 50 years of age, when sufficient iron has accumulated to cause organ damage. Significant end-organ damage is unlikely if ferritin levels are <1000 ng/mL.

A common early sign of iron overload leading to end-organ damage is elevation of liver enzyme levels, which later may be accompanied by recurrent right sided abdominal pain and hepatomegaly. Arthropathy is also common, and occasionally acute episodes of inflammatory arthritis occur. Other early signs can include impotence, amenorrhea, irritability, depression, and fatigue. Because these clinical conditions are not specific to iron overload, the disorder may go undetected and not considered in the differential diagnosis.

Patients that are diagnosed at the pre-cirrhotic, pre-diabetic stage and treated to remove the excess iron can have a normal life expectancy. Once diabetes mellitus and/or cirrhosis have developed, a shortened life expectancy will likely occur and if cirrhosis is present, there is a higher risk of liver cancer even when iron depletion has been achieved.

Because of its genetic nature, first degree relatives of those with definitively diagnosed HFE hemochromatosis should be identified and tested.

PATIENTS AT RISK FOR HFE HEMOCHROMATOSIS

- First degree relatives of those with definitively diagnosed HFE hemochromatosis
 - Siblings of an affected individual are at 25% risk of having the same genetic constitution. Offspring are at least obligate carriers but may also be at risk for a significant genetic constitution if their affected parent has, by chance, married a carrier.⁷
- Individuals with unexplained abnormalities suggestive of end-stage organ damage from excessive iron stores, especially liver function abnormalities
 - As mentioned, however, there are many more common causes of cirrhosis, congestive heart failure, diabetes, arthropathy, skin discoloration and endocrine insufficiencies than end-stage organ damage from HFE hemochromatosis.
- It is controversial whether individuals of Northern European heritage should be screened in middle age similar to screening for other preventable disorders such as hypertension, diabetes and hyperlipidemia. One school of thought is that as this is a preventable disorder, screening should be offered to the target population i.e., northern Europeans. Conversely, the argument is made that too few individuals with a genetic predisposition will ever develop serious end-organ disease to justify screening of this population.

SCREENING

CLINICAL SCREENING FOR HEMOCHROMATOSIS

A high index of suspicion is essential as none of the end-organ disorders are pathognomonic for hemochromatosis. Prior to diagnosis, the only significant differences in history and physical between those with genetic predisposition and those without, is an excess of liver function abnormalities amongst the former.⁷ The most obvious clue is a family history of a definitively diagnosed case. Other occurrences which should raise high suspicion include unexplained cirrhosis or liver cancer.

The best objective laboratory screen is the % transferrin saturation combined with serum ferritin.⁶ Reproducible results (on two or more occasions) of iron saturation > 45% is suspicious for possible hemochromatosis, especially if combined with ferritin elevated above standard norms (>300ng/mL in men and >200 ng/mL in women.)⁶ Elevated ferritin BY ITSELF is not an appropriate screening tool as ferritin is an acute phase reactant and may be elevated in acute or chronic infectious, inflammatory and neoplastic conditions. The hemoglobin and hematocrit are useful only in timing of phlebotomies. Hemochromatosis does NOT cause polycythemia. A normal transferrin saturation percent with an elevated ferritin may require further investigation.

GENETIC TESTING

PATIENTS REQUIRING GENETIC TESTING

- First degree relatives of individuals with definitely diagnosed HFE hemochromatosis⁶
- Those with a persistently elevated transferrin saturation level at or above levels of suspicion, particularly in the presence of elevated ferritin

End-organ symptoms most commonly occur in patients with C282Y/C282Y, rarely in patients with C282Y/H63D and almost never in patients with H63D/H63D.

BENEFITS AND RISKS OF GENETIC TESTING

The major advantage of genetic testing is to prevent excessive iron storage and therefore end stage organ damage. Individuals with the genetic predisposition to develop end-organ damage can prevent this by maintaining iron stores at normal levels. Even symptomatic disease can be improved to some degree although the risk for hepatocellular carcinoma cannot be removed if liver damage has already occurred.

The major risk for genetic testing is life and disability insurance discrimination for anyone diagnosed pre-symptomatically with a genetic predisposition. This could affect opportunities and/or ability to emigrate to, or obtain health care insurance in other countries.

GENETIC COUNSELLING

Before any molecular diagnostic test is performed, the patient must be fully informed of the following:

1. Limitations of the test. In this scenario, the only genetic condition that will be diagnosed is HFE hemochromatosis. This is the only genetic test for hemochromatosis currently available, and will not diagnose other types of genetic or acquired hemochromatosis. The genetic test cannot predict who specifically will develop end-organ disease.
2. The risks and benefits of testing must be clearly outlined particularly with risks of discrimination as described above. Testing of children under the age of 18 years is not performed as iron overload is rare in this age group and potential for insurance discrimination outweigh the benefits.

Use the Molecular Diagnostic laboratory requisition for Edmonton or Calgary to order the test. Results are available between four to eight weeks. The test costs \$250 and is covered by Alberta Health.

Genetic counselling may be performed by Medical Genetics via referral or by the ordering physician.

MANAGEMENT

TREATING PATIENTS WITH HFE HEMOCHROMATOSIS

For those patients with evidence of end-organ damage, it is recommended to reduce their ferritin levels to 50-100 ng/mL while maintaining a hemoglobin above 110 g/L. Initially, phlebotomy should be performed weekly to biweekly; however, the frequency will vary with each individual therefore blood work should be carried out prior to each phlebotomy.

If the patient has no evidence of end-organ damage, it is recommended to reduce ferritin levels to <300 ng/mL for males and <200 ng/mL for females, while maintaining a hemoglobin above 110 g/L.⁶

An asymptomatic patient with iron overload, who is otherwise eligible to be a blood donor, is recommended to become a regular blood donor at Canadian Blood Services. This may be adequate to keep ferritin and hemoglobin at recommended levels for those patients with an early diagnosis but those with more advanced cases may require more frequent phlebotomy.

OTHER RECOMMENDATIONS FOR PATIENTS

- ✓ Reduce exogenous iron:
 - Avoid dietary supplements with iron
- ✓ Reduce coincident risks to end-organs:
 - Frequent excessive alcohol intake

LIVER BIOPSY

Liver biopsy is no longer necessary to diagnose HFE hemochromatosis, but it may be necessary to stage the degree of liver damage or to diagnose hepatocellular carcinoma. For non HFE hemochromatosis-related cirrhosis, liver biopsy is necessary to make a correct diagnosis.

TREATING END-ORGAN DISEASE/FAILURE

Phlebotomy to achieve appropriate ferritin levels will improve some symptoms among most individuals, but this is not predictable. Specific end-organ disease should be treated as per usual protocols for cirrhosis, diabetes, heart failure, hypothyroidism, etc.

PATIENT WITH ELEVATED PERCENT TRANSFERRIN SATURATION AND FERRITIN BUT NORMAL GENETIC TEST RESULT (OR CARRIER)

There are two possible scenarios:

1. The patient may have an acquired form of hemochromatosis that has not been appreciated and one should review the patient’s clinical history for other causes.
2. In the absence of any known acquired cause, the patient may have a rare form of genetic hemochromatosis that cannot yet be diagnosed by molecular means. The risk of symptomatic end-organ disease is not known and risk to relatives cannot be estimated. It is reasonable to assume that excessive iron stores from any cause are potentially detrimental to health and treatment as outlined for HFE hemochromatosis would still be recommended. Percent transferrin saturation and ferritin levels would be recommended for first degree relatives.

Note: This applies ONLY when BOTH percent transferrin saturation and ferritin are elevated in the setting of a non-informative molecular diagnostic.

REFERRALS

FOR GENETIC CONCERNS:

Edmonton Medical Genetics Clinic
 8-53 Medical Sciences Building, University of Alberta
 Edmonton AB T6G 2H7
 Phone: 780.407.7333 Fax 780.407.6845

Calgary Medical Genetics Clinic
 Alberta Children’s Hospital
 2888 Shagannapi Trail NW
 Calgary AB T3B 6A8
 Phone: 403.955.7373 Fax 403.955.2701

REFERENCES

1. Kowdley KV, Bennett RL, Motulsky A. Current. HFE-Associated Hereditary Hemochromatosis Gene Reviews <http://www.ncbi.nlm.nih.gov/books/NBK1440#hemochromatosis>
2. Phatak PD, Bonkovsky HL, Kowdley KV. Hereditary hemochromatosis: time for targeted screening. *Ann Intern Med.* 2008;149:270-2.
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;352:1769-78.
4. Gordeuk VR. African iron overload. *Semin Hematol.* 2002;39:263-9.
5. Allen KJ, Gurrin LC, Constantine CC, Osborne NJ, Delatycki MB, Nicoll AJ, et al. Iron-overload-related disease in HFE hereditary hemochromatosis. *N Engl J Med.* 2008;358:221-30.
6. Bacon, Uptodate online®.
7. van Bokhoven MA, van Deursen CThBM, Swinkels DW. Diagnosis and management of hereditary haemochromatosis. *BMJ.* 2011;342:218-23.

SUGGESTED CITATION

Toward Optimized Practice (TOP) Hemochromatosis Working Group. 2010 February. Diagnosis and management of hemochromatosis clinical practice guideline. Edmonton, AB: Toward Optimized Practice. Available from: <http://www.topalbertadoctors.org>

For more information see www.topalbertadoctors.org

GUIDELINE COMMITTEE

The review committee consisted of representatives of hematology in Edmonton and the revised content was reviewed by a primary care physician with expertise in evidence-based medicine.

February 2007

Reviewed February 2008

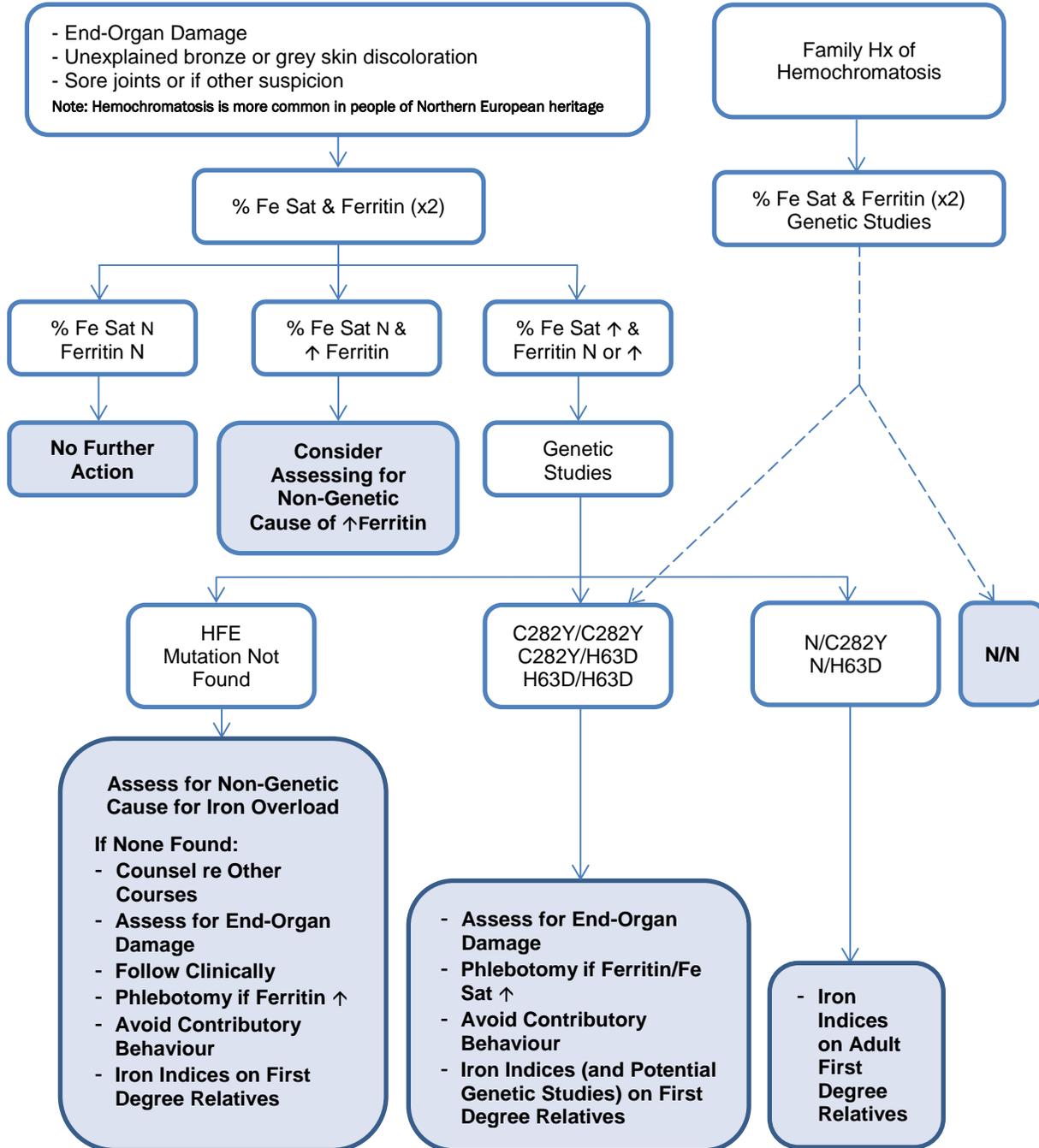
Reviewed February 2010

Minor Revision December 2014

Minor Revision February 2016 (typo in algorithm)

ALGORITHM

Algorithm for Clinical Suspicion of HFE Hemochromatosis



These recommendations are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. They should be used as an adjunct to sound clinical decision making.