# Hemochromatosis

## *Common genes, uncommon illness?*

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ABSTRACT

**OBJECTIVE** To increase family physicians' awareness of the prevalence of hemochromatosis and to suggest strategies for diagnosis and management of hemochromatosis with the goal of decreasing the development of associated life-threatening conditions.

**QUALITY OF EVIDENCE** A MEDLINE search from January 1966 to January 2002 using the MeSH term hemochromatosis/therapy found no randomized controlled trials. A further search from January 1990 to January 2002, using the heading hemochromatosis and subheadings diagnosis, epidemiology, genetics, and therapy, found articles with level II evidence (case-control and cross-sectional studies) and level III evidence (descriptive studies and reports from expert committees). Articles were selected based on clinical relevance.

**MAIN MESSAGE** Hemochromatosis is the most common hereditary condition in populations of Northern European descent, affecting three to five people per thousand. Many of these people remain undiagnosed with this condition. The iron overload associated with hemochromatosis can lead to serious, life-threatening conditions, such as diabetes, hepatic cirrhosis, primary liver cancer, and cardiomyopathy. Family physicians can screen patients they suspect are at risk of hemochromatosis with simple indirect serum iron measurements (transferrin saturation and serum ferritin) and with widely available genetic tests (C282Y and H63D). Studies of families can help uncover further cases of hemochromatosis; population screening is currently under study.

**CONCLUSION** Family physicians can facilitate early diagnosis of hemochromatosis by maintaining a high index of suspicion in patients with early signs or symptoms or in high-risk groups, and screening these patients for hemochromatosis.

RÉSUMÉ

**OBJECTIF** Conscientiser le médecin de famille à la prévalence de l'hémochromatose et suggérer des stratégies de diagnostic et de traitement de cette maladie dans le but de retarder le développement de complications éventuellement mortelles.

**QUALITÉ DES DONNÉES** Une première recherche sur MEDLINE entre janvier 1966 et janvier 2002 à l'aide du terme MeSH anglais hemochromatosis/therapy n'a pas retracé d'essai thérapeutique randomisé. Une seconde recherche entre janvier 1990 et janvier 2002 à l'aide de la rubrique hemochromatosis et des sous-rubriques diagnosis, epidemiology, genetics et therapy a trouvé des articles avec preuves de niveau II (études de cas avec témoins et études transversales) et avec preuves de niveau III (études descriptives et rapports de comités d'experts). Seuls les articles ayant un intérêt clinique ont été retenus.

**PRINCIPAL MESSAGE** L'hémochromatose est la maladie héréditaire la plus fréquente chez les personnes de descendance nord-européenne, où elle touche de trois à cinq personnes par mille. Dans plusieurs cas, la maladie n'est pas diagnostiquée. La surcharge en fer qui caractérise cette maladie peut entraîner des conditions éventuellement fatales telles un diabète, une cirrhose du foie, un cancer primitif du foie et une myocardiopathie Le médecin de famille peut faire le dépistage de l'hémochromatose chez les patients qu'il croit porteurs par une simple mesure indirecte du fer sérique (saturation de la transferrine et ferritine sérique) et par des tests génétiques largement accessibles (C282Y et H63D). L'étude des familles peut servir à révéler d'autres cas d'hémochromatose; on étudie présentement la possibilité d'un dépistage de population.

**CONCLUSION** Un diagnostic précoce d'hémochromatose est possible à la condition que le médecin de famille garde cette possibilité à l'esprit en présence de groupes à risque élevé ou de patients qui en manifestent les signes ou symptômes précoces et qu'il effectue un dépistage d'hémochromatose chez ces patients.

*This article has been peer reviewed.*
*Cet article a fait l'objet d'une évaluation externe.*
*Can Fam Physician* 2002;48:1326-1333.

Hereditary hemochromatosis is the most common known genetic disorder in populations of Northern European descent, affecting three to five people per thousand.[1] The genetic basis for this condition, discovered by Feder and associates in 1996, consists of a mutation of the *HFE* gene on the short arm of chromosome 6.[2] This missense mutation, in which tyrosine is substituted for cysteine at amino acid 282 of the protein product, has been found in more than 90% of patients with clinically defined hemochromatosis, most of whom are homozygous for this variant of the gene.[3]

A second mutation at amino acid 63, in which aspartic acid is substituted for histidine (H63D), also plays a role in development of iron overload, but its effect is less clear. There might be other, as yet undiscovered, genes that contribute to hemochromatosis, and studies are under way to investigate this possibility.

Transmission of the condition follows an autosomal recessive mode of inheritance. Patients with hemochromatosis have abnormal iron metabolism; they absorb iron from the diet much faster than people whose metabolism is normal do.[4] Sequelae associated with accumulation of iron in body organs include diabetes, hepatic cirrhosis, primary liver cancer, and cardiomyopathy.[5] Development of these conditions leads to a shorter life expectancy among patients with hemochromatosis.

Because symptoms often indicate severe iron overload, hemochromatosis needs to be detected early, ideally before patients show symptoms. Simple treatment with phlebotomy can effectively prevent development of more serious conditions. In a typical Canadian family physician's practice of 2000 patients, five to 10 people will be C282Y homozygotes, the typical genetic pattern of hereditary hemochromatosis. Family physicians should think about screening patients for this condition if they consider a diagnosis of hemochromatosis in patients who present with the typical early symptoms (**Table 1**), and should offer genetic testing to family members of patients discovered to be C282Y homozygotes.

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**Table 1. Signs and symptoms of hemochromatosis**

| |
|---|
| **EARLY SYMPTOMS** |
| Fatigue |
| Arthralgia, especially in hands |
| **LATE SYMPTOMS** |
| Similar to those associated with: |
| • Cirrhosis |
| • Diabetes |
| • Heart failure |
| Impotence |
| **SIGNS** |
| Increased skin pigmentation, especially bronze or gray |
| Hepatomegaly with or without elevated alanine aminotransferase or aspartate aminotransferase levels |

### Quality of evidence

A MEDLINE search from January 1966 to January 2002 using the MeSH term hemochromatosis/therapy failed to find any randomized controlled trials. A further search from January 1990 to January 2002, using the heading hemochromatosis and the subheadings diagnosis, epidemiology, genetics, and therapy, found articles with level II (case-control and cross-sectional studies) and level III (descriptive studies and reports from expert committees) evidence. Articles were selected based on their direct relevance to the prevalence, diagnosis, and treatment of hereditary hemochromatosis.

Reports from expert committees included a practice guideline commissioned and approved by the American Association for the Study of Liver Diseases published in 2001[6] and a report of the European Association for the Study of the Liver's (EASL's) International Consensus Conference on Haemochromatosis published in 2000.[7] Both of these were based on careful consideration of the best evidence available to inform the recommendations of the respective expert groups (level II and III evidence).

### Is hemochromatosis a rare disease?

Hemochromatosis can present a diagnostic challenge. Symptoms are often vague and can be easily attributable to other conditions. Iron overload is rarely high on the list of differential diagnoses for patients presenting with fatigue, arthropathy, or symptoms suggesting diabetes. Interestingly, iron overload is often discovered incidentally when investigating fatigue or weakness by measuring serum ferritin. Levels are unexpectedly high instead of low.

Many family physicians assert that, in their years of practice, they have never encountered a case of hemochromatosis. This seems impossible based on the findings of studies in several countries that indicate that about one in 300 people have the genetic pattern associated with hereditary hemochromatosis.[8-10] Despite these findings, however, hemochromatosis is diagnosed at a significantly lower rate, at about one in 10 000 people.[7] Two possible explanations for this discrepancy are underdiagnosis and lack of complete penetrance, or "expressivity," of the genes for hemochromatosis. Discovery of the gene has created a dilemma for case definitions of hemochromatosis using genotype or phenotype, and a consistent definition that all experts can agree on has yet to be developed.

A phenotypic case definition depends on the degree of iron overload determined by either liver biopsy or quantitative phlebotomy (number of phlebotomies required to deplete iron stores). This definition would include all types of iron overload, including secondary iron overload (**Table 2**). Using a phenotypic definition ensures a high sensitivity for biochemical screening tests.

A genotypic case definition is simple and precise, but the prevalance of "non-expressing" (no biochemical or clinical evidence of iron overload) C282Y homozygotes could be as high as 50%.[11] It is unclear whether a non-expressing C282Y homozygote should be considered as having the earliest stage of hemochromatosis.[7]

Several studies have attempted to estimate the penetrance of the gene. A large population study by Olynyk et al[12] in 1999 found that 58% of C282Y homozygotes went on to develop progressive iron overload. Other researchers have found biochemical expression to be in the range of 50% to 90%, with men more likely to develop iron overload than women.[13] Women might develop milder iron overload and develop it later due to blood loss during menstruation and childbirth.

**Table 2. Differential diagnosis of iron overload**

| |
|---|
| **HEMOCHROMATOSIS RELATED TO THE HFE GENE** |
| (In Canada, it accounts for >90% of cases of clinically diagnosed hemochromatosis.) |
| C282Y homozygotes (95%) |
| C282Y/H63D compound heterozygotes (4%) |
| H63D homozygotes (1%) |
| **HEMOCHROMATOSIS NOT RELATED TO THE HFE GENE** |
| Transferrin receptor 2 mutation (rare) |
| Ferroportin mutation (rare) |
| Nonfamilial (might be a heterogeneous collection of conditions resulting in iron overload) |
| Juvenile hemochromatosis (young adults with cardiac and endocrine dysfunction) |
| Neonatal hemochromatosis |
| **MISCELLANEOUS IRON OVERLOAD** |
| African-American iron overload |
| African iron overload |
| Polynesian iron overload |
| Transfusional iron overload |
| Iron overload related to insulin resistance |
| Aceruloplasminemia (rare) |
| Alcoholic siderosis |
| Iron overload secondary to end-stage cirrhosis |
| Porphyria cutanea tarda |
| Post-portacaval shunt |

**When should hemochromatosis be suspected?**

Symptoms of hemochromatosis are often vague. Early symptoms include generalized weakness and arthralgia, particularly of the hands. Later symptoms are similar to those associated with cirrhosis, diabetes, and heart failure (**Table 1**).[7] Other signs and symptoms include impotence, increased skin pigmentation, hepatomegaly, and elevated levels of aspartate aminotransferase (AST). A large screening study in San Diego reported that the prevalence of these nonspecific symptoms is similar in C282Y homozygotes and control patients. This might be related to the fact that they screened relatively asymptomatic subjects and to the method of assessing liver disease, which was unconventional.[9]

Because its early symptoms are nonspecific, hemochromatosis should be added to the list of possible causes of fatigue, arthropathies, and the signs and symptoms resulting from organ damage due to iron deposition. The report of the EASL's International Consensus Conference on Haemochromatosis[7] included recommendations that physicians be encouraged to order serum iron tests (such as transferrin saturation) for patients with chronic parenchymal liver diseases, cardiomyopathy and arrhythmias, diabetes types 1 and 2, impotence and loss of libido, infertility, and arthritis or arthralgia, among others (level III evidence) (**Table 3**). Family members of patients with confirmed hemochromatosis should be assessed for evidence of iron overload, whether or not they have symptoms.

**Table 3. Conditions associated with hemochromatosis:** *Physicians should consider ordering serum iron tests for patients with these conditions*

| |
|---|
| Arthritis or arthralgia |
| Arrhythmias |
| Chronic parenchymal liver diseases |
| Cardiomyopathy |
| Diabetes types 1 and 2 |
| Impotence and loss of libido |
| Infertility |

Hereditary hemochromatosis should be considered in anyone with elevated transferrin and ferritin levels, even if there appears to be another etiology, such as viral hepatitis. In one study, seven of nine homozygotes would not have been discovered if researchers had stopped investigations because they found a reason for secondary iron overload.[14] Assessment of patients with high levels of iron should include questions about symptoms of liver disease, arthritis, impotence or infertility, heart failure, bronzed skin, blood transfusions or donations, ethnic background, inflammatory or autoimmune conditions, anemia, alcohol use, and history of malignancy.

### Which screening tests are best for hemochromatosis?

Screening tests fall into two categories: those that test for phenotypic, or biochemical, evidence, and those that assess genetic predisposition. The most commonly used phenotypic tests are serum ferritin and transferrin saturation (**Table 4**).

Serum ferritin is usually well correlated with total body iron stores.[15] Iron overload is highly unlikely with normal serum ferritin levels. Ferritin is a first-phase reactant, however, and can become elevated in the presence of inflammation, cytolysis, and malignancy. These processes must be considered when interpreting serum ferritin test results. Common causes of mild elevations in ferritin are a fatty liver and regular alcohol consumption.

Transferrin saturation at a threshold of >45% was found to have a sensitivity of 94% for diagnosing C282Y hemochromatosis in an Australian screening study.[12] There is a diurnal variation in transferrin levels; the most accurate values can be obtained after an overnight fast.[16] When the fasting value is >50% for women and >60% for men, transferrin levels have a sensitivity of 92%, a specificity of 93%, and positive predictive value of 86% for diagnosing hemochromatosis in referred patients.[6] Some large population studies, however, have demonstrated a sensitivity of only 52% to 60% for detection of C282Y homozygotes. This can be explained by the large number of non-expressing cases.[10,17]

### When should genetic tests be ordered?

The practice guidelines of the American Association for the Study of Liver Diseases recommend genetic testing to detect *HFE* mutations for all people with abnormal iron levels (transferrin >45%; serum ferritin >200 μg/L for women and >300 μg/L for men) and for all first-degree relatives (parents, siblings, and offspring) of identified C282Y homozygotes.[6] Siblings of homozygotes are at greater risk of being homozygotes themselves (one in four chance) than their children are (about one in 20 chance).[18] The genetic test is done at most provincial DNA diagnostic laboratories at no cost to patients.

### How is the genetic test interpreted?

Test results indicate whether any C282Y or H63D mutations were detected, and if so, whether patients are homozygous or heterozygous for these genotypes (**Table 5**). Patients at highest risk of iron overload are those who are homozygous for the C282Y mutation.[10] These patients have about a 50% chance of developing biochemical evidence of iron overload. Men are at higher risk than women.[8] The other two genotypes at risk of iron overload are compound heterozygotes (heterozygous for both C282Y and H63D), who have a 2% risk, and H63D homozygotes, who have a 1% risk.[19]

**Table 4. Ranges of serum ferritin and transferrin saturation and costs of testing**

| MEASURE | NORMAL RANGE | POSSIBLE IRON OVERLOAD | COST ($) BRITISH COLUMBIA | ALBERTA | ONTARIO | QUEBEC |
|---|---|---|---|---|---|---|
| Serum ferritin | 22-322 (μg/L) (men)<br>10-291 (μg/L) (women) | >300 (μg/L) (men)<br>>200 (μg/L) (women) | 28.80 | 11.00 | 20.68 | 18.80 |
| Transferrin saturation | 20%-50% | >50% (men)<br>>45% (women) | 22.73 | 21.85 | 17.58 | 15.50 |

*Information from MDS Laboratories, Toronto, Ont.*

**Table 5. Interpretation of genetic testing for hemochromatosis**

**C282Y HOMOZYGOTE**
Classic genetic pattern seen in >90% of typical cases. Patient carries two copies of the major mutation of the *HFE* gene. Expression of disease ranges from no evidence of iron overload to massive iron overload with organ dysfunction. Siblings have a one in four chance of being affected and should have genetic testing. For children to be affected, the other parent must be at least a heterozygote. If iron levels are normal, physicians should consider false-positive test results or a non-expressing homozygote.

**C282Y-H63D (COMPOUND HETEROZYGOTE)**
Patient carries one copy of the major mutation and one copy of the minor mutation. Most patients with this genetic pattern have normal iron levels. A few compound heterozygotes have been found to have mild-to-moderate iron overload. Heavy iron overload is usually seen when there is a concomitant risk factor (alcoholism, viral hepatitis)

**C282Y HETEROZYGOTE**
Patient carries one copy of the major mutation. This pattern is seen in about 10% of white people and is usually associated with normal iron levels. In rare cases, iron levels are as high as those expected in homozygotes. These patients could carry an unknown hemochromatosis mutation. Liver biopsy can help determine the need for venesection therapy.

**H63D HOMOZYOTE**
Patient carries two copies of the minor mutation. Most patients with this genetic pattern have normal iron levels; a few have been found to have mild-to-moderate iron overload. Severe iron overload is usually seen when there is a concomitant risk factor (alcoholism, viral hepatitis).

**H63D HETEROZYGOTE**
Patient carries one copy of the minor mutation. This pattern, seen in about 20% of white people, is usually associated with normal iron levels, and is so common in the general population that the iron overload could be related to another risk factor. Liver biopsy might be required to determine the cause of the iron overload and the need for treatment.

**NO *HFE* MUTATIONS**
Other iron overload diseases are associated with mutations in other iron-related genes (transferrin receptor 2, IREG1). Other hemochromatosis mutations will likely be discovered in the future. If a patient has iron overload and no *HFE* mutations, physicians should take a careful history for other risk factors and perhaps order a liver biopsy to determine the cause of the iron overload and the need for treatment. Most of these patients are isolated, nonfamilial cases. There have been cases of familial iron overload associated with other non–*HFE* mutations (TfR2 mutation, ferroportin mutation).

### Who needs a liver biopsy?

Before the advent of genetic tests, diagnosis of hemochromatosis was confirmed by substantial iron deposition in the parenchymal cells of the liver found at liver biopsy. With the widespread availability of the genetic test, liver biopsy has become more useful for prognosis than diagnosis. The main prognostic determinant is presence or absence of cirrhosis at diagnosis or at initiation of treatment.[20] Cirrhosis is not reversed with phlebotomy, and life expectancy cannot be restored to normal when it is present. Cirrhotic patients have a 200-fold risk of hepatocellular carcinoma compared with normal patients.[21] These patients should be monitored for hepatocellular carcinoma with ultrasound examinations of the liver about every 6 months.

Patients who are C282Y homozygotes and who have evidence of liver dysfunction (AST >40 U/L) or ferritin levels >1000 μg/L) should be considered for liver biopsy (level II evidence). Guyader et al[22] found no notable liver fibrosis in C282Y homozygous patients with serum ferritin levels <1000 μg/L who had no hepatomegaly and normal serum transaminase levels.[22] Liver biopsy is most important for diagnosing non–*HFE*-related iron overload in patients with concomitant risk factors (**Figure 1**).

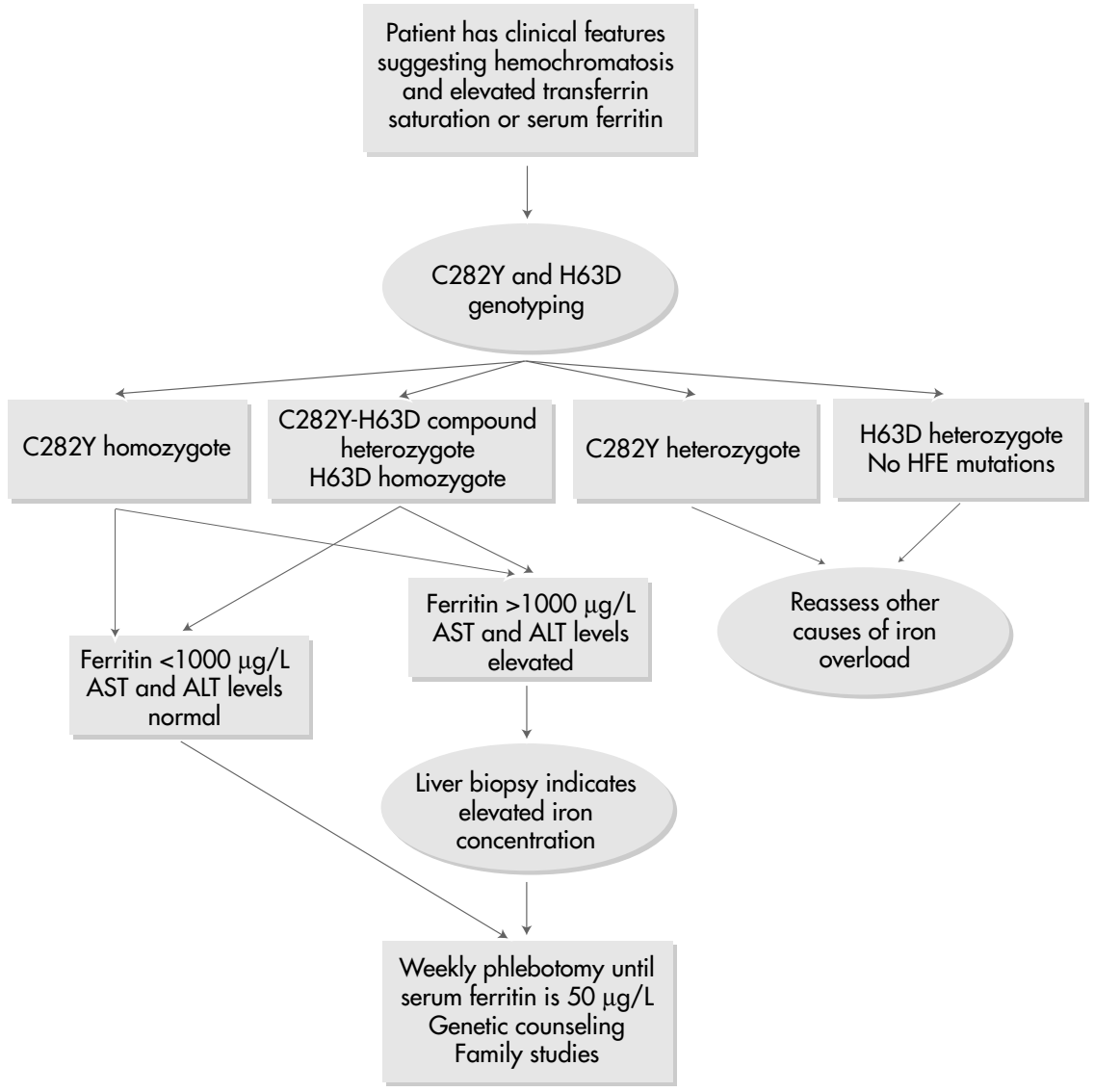
### Treatment

Phlebotomy is the usual treatment for C282Y homozygotes with serum ferritin levels >200 μg/L (women) or >300 μg/L (men) and transferrin saturation >45% (women) or >50% (men). These patients might need to be referred to a centre that offers this treatment.

Treatment removes 450 to 500 mL of blood every week until ferritin levels are in the low-normal range (20 to 50 μg/L). Hemoglobin is measured at the time of each phlebotomy; if it falls below 100 g/L, phlebotomy frequency is decreased to once every 2 weeks. Once the ferritin level is in the low-normal range, maintenance therapy with less frequent phlebotomy (often around 3 to 4 times per year) is begun.[23]

In Canada, blood from hemochromatosis patients is accepted for donation (as long as other criteria are met). Patients can be advised to become voluntary blood donors several times per year. Niederau and associates[20] have found phlebotomy to be highly effective therapy for hemochromatosis; it appears to lower morbidity and promote normal longevity. Symptoms can improve differentially during treatment. Positive effects are more often noted with fatigue, symptoms of cardiomyopathy, and skin pigmentation than with arthritis.

**Figure 1.** Diagnosis and management of hemochromatosis




ALT—alanine aminotransferase, AST—aspartate aminotransferase.

Compliance with phlebotomy is usually high, estimated in the range of 70% to 84%.[24] To date, no controlled trials have randomized patients to phlebotomy or no treatment. This could be considered unethical because the current treatment is thought to be effective and well tolerated, and because withholding treatment might increase patients' risk of adverse effects. Chelation is not used for treating hereditary hemochromatosis due to its unpleasant route of administration and side effects. Dietary restrictions are not necessary, but patients are advised not to ingest iron supplements or high doses of vitamin C (500 mg).

**How is a family investigated?**

A family study begins with obtaining a family tree from patients with as much information about the health of each family member as possible. It is a

challenge to impress upon patients the potential seriousness of this condition and to have them convey this to their families. Ideally, patients will inform their own families about the condition and the need to be tested.

Family members might be able to come in together for blood tests and some counseling, although care must be taken to maintain confidentiality. Sensitive information, such as paternity issues, could come to light during a family study. Clinicians must be prepared to deal with them appropriately.

### Should the entire population be tested?

Routine screening for hemochromatosis is not yet included in the recommendations of the Canadian Task Force on Preventive Health Care. Although hemochromatosis meets many World Health Organization criteria for appropriate diseases to screen for, we still do not know enough about the burden and natural history of the disease.[13] Genetic screening has not been advocated because detecting patients who might never express the disease raises several psychosocial issues, such as potential genetic discrimination by employers and insurance agencies, complicated family dynamics, and stigmatization. A study of more than 5000 volunteer blood donors found no adverse psychosocial effects of genetic testing among them.[25]

Despite these difficulties, evidence is mounting that hemochromatosis might be a condition for which certain groups in the general population should be screened. With the low cost of the biochemical tests and the decreasing cost of the genetic test, screening for hemochromatosis could become a cost-effective strategy.[26] The Hemochromatosis and Iron Overload Screening (HEIRS) study plans to sample 100 000 people in Canada and the United States for hemochromatosis and iron overload using both phenotypic and genotypic tests. A large component of the study is investigating the ethical, legal, and social implications of genetic testing.[8] We hope the findings from this study will further inform the decision to screen or not to screen the general population.

### Conclusion

Hereditary hemochromatosis is a genetic condition with a substantial prevalence in Canada and other countries that have a high percentage of their populations of European descent. Early treatment has been shown to lead to improved outcomes and longer life expectancy. Timely diagnosis can be a challenge. More information about

### Editor's key points

- Despite being the most common hereditary (autosomal recessive) condition in Northern Europeans (one case per 200 to 300 people), rates of diagnosis are considerably lower than expected.
- The consequences of unrecognized hemochromatosis include the complications of iron overload: hepatic cirrhosis, diabetes, cardiomyopathy, and hepatic cancer.
- Presenting symptoms, such as fatigue, arthropathy, and loss of libido, tend to be vague, and hemochromatosis does not rank high on the list of differential diagnoses.
- New genetic tests for the C282Y chromosome can clearly identify those with an increased predisposition for hemochromatosis, but not all cases show the markers of the disease. Currently, widespread screening is not recommended.
- Making a diagnosis in a timely manner is important, because complications can be prevented by active treatment with phlebotomy.

### Points de repère du rédacteur

- Même si l'hémochromatose est l'affection héréditaire à caractère autosomique récessif la plus fréquente chez les habitants d'Europe du Nord (un cas sur 200 à 300 personnes), cette maladie demeure largement sous-diagnostiquée.
- Parmi les conséquences de cette carence de diagnostic, mentionnons les complications reliées à la surcharge en fer: cirrhose du foie, diabète, myocardiopathie et cancer du foie.
- Les symptômes initiaux tels fatigue, arthropathies et baisse de la libido sont plutôt vagues; d'autre part, l'hémochromatose n'occupe pas un rang très élevé dans les choix possibles lors du diagnostic différentiel.
- Les personnes qui ont une prédisposition accrue à l'hémochromatose peuvent être clairement identifiées grâce aux nouveaux tests génétiques pour le chromosome C282Y, quoique le marqueur de la maladie ne soit pas présent chez tous les sujets atteints. À l'heure actuelle, on ne préconise pas un dépistage à grande échelle.
- Il est important de poser ce diagnostic à temps puisqu'un simple traitement par des phlébotomies répétées peut prévenir les complications.

the burden and natural history of the disease, and the psychosocial effect of population screening are needed. Family physicians can facilitate early diagnosis by maintaining a high index of suspicion in patients with early signs or symptoms of the disease or in high-risk groups and by screening them for hemochromatosis.

### Competing interests

*None declared*

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