Hemochromatosis: What every clinician and health care professional needs to know is an online training course for primary care providers describing the pathophysiology, epidemiology, diagnosis, treatment, and management of patients with adult onset hemochromatosis.

If you are looking for basic information about hemochromatosis and hereditary hemochromatosis, visit the CDC Web site Iron Overload and Hemochromatosis for information designed to assist patients and their families maintain healthy lifestyles.

Overview of the Disease

The disease hemochromatosis, a disorder of iron metabolism, occurs as a result of excess iron accumulation in tissues and organs. If left undiagnosed and untreated, iron overloading can cause serious and sometimes fatal health problems. Early detection of iron overload and hemochromatosis treatment can delay or prevent irreversible complications and prolong life.

- Early non-specific symptoms of hemochromatosis (e.g., fatigue, arthralgias, weakness, weight loss, abdominal pain) often resemble symptoms of various other diseases.
- The diagnosis of hemochromatosis is often missed, especially when the disease is in its early stages.
- Delay in diagnosis results in an increase of related health problems, including permanent organ damage.
- Hemochromatosis can be detected with simple blood tests.
- The treatment of choice, phlebotomy, is relatively easy and inexpensive.

Health care professionals therefore, need to maintain a high index of suspicion for patients with early non-specific symptoms of this disease.

Continuing Education

Free continuing education credit is available for physicians, nurses, and health educators. Click here to register. The course requires approximately two hours to complete.

Purpose of the Course

Hemochromatosis experts at the Centers for Disease Control and Prevention and medical experts throughout the United States developed this course to promote early detection and early intervention of adult onset hemochromatosis. List of Faculty.

Course Objectives:

- Recognize signs and symptoms of hemochromatosis.
- Identify the recommended procedures for diagnosing hemochromatosis.
- Identify an initial course of treatment for patients.
- Counsel patients with hemochromatosis on family based detection.

Course Modules

PATHOPHYSIOLOGY MODULE

Assessment of patients with vague, non-specific symptoms (e.g., fatigue, weakness, and arthralgia) presents a challenge to the primary care professional. A possible underlying cause, iron overload, is often missed.

Early detection of iron overload and hemochromatosis treatment can delay or prevent irreversible complications and prolong life.

> "Following discovery of the hereditary hemochromatosis gene known as *HFE*, the significance of genes in hemochromatosis was overstated by researchers and advocacy groups alike. Witness the claim: "hemochromatosis is the most common genetic disease known…" Actually, hemochromatosis is not the most common genetic disease known; rather it is a disease that illustrates the limitations of genetic testing. For example, the *HFE* genetic test is unlikely to be cost effective for large scale screening for hemochromatosis. Genetic testing should not distract people from the fundamental principle that hemochromatosis is about iron."
>
> David G. Brooks, MD, PhD
> Division of Medical Genetics
> Department of Medicine
> University of Pennsylvania

Content in this module includes

- Iron overload and its relation to hemochromatosis.
- *HFE* gene mutations affect on iron absorption.
- Hereditary hemochromatosis.

Review of Normal Iron Storage and Absorption

Iron facts

- All body cells need iron. It is crucial for oxygen transport, energy production, and cellular growth and proliferation.
- The human body contains an average of 3.5 g of iron (males 4 g, females 3 g);
- The typical daily American diet contains 10-20 mg of iron.
- Only about 10% of dietary iron is absorbed (1-2 mg/day).

Iron absorption

- Iron is mainly absorbed in the duodenum and upper jejunum.
- A protein called divalent metal transporter 1 (DMT1) facilitates iron transfer across intestinal epithelial cells.
- Normally, individuals absorb less than 10% of dietary iron, or 1-2 mg per day balancing the daily loss from desquamation of epithelia.
- Most absorbed iron is used in bone marrow for erythropoiesis.
- Iron homeostasis is closely regulated via intestinal absorption.

- Once iron is absorbed, there is no physiologic mechanism for excretion of excess iron from the body other than blood loss (i.e., pregnancy, menstruation or other bleeding).

Iron transport

- Most absorbed iron is transported in the bloodstream bound to the glycoprotein **transferrin**.
- Transferrin is a carrier protein that plays a role in regulating the transport of iron from the site of absorption to virtually all tissues.
- Transferrin binds only two iron atoms.
- Normally, 20-45% of transferrin binding sites are filled (measured as percent transferrin saturation [TS]).

Iron use in the body

- 75% of absorbed iron is bound to proteins such as hemoglobin that are involved in oxygen transport.
- About 10% to 20% of absorbed iron goes into a storage pool that is also recycled in erythropoiesis, so storage and use are balanced.

Iron storage

- Iron is initially stored as **ferritin**.
- A single ferritin molecule can store up to 4,000 iron atoms.
- When excess dietary iron is absorbed, the body responds by producing more ferritin to facilitate iron storage.

Iron overload

Iron overload is the accumulation of excess iron in body tissues.

Iron overload usually occurs as a result of a genetic predisposition to absorb iron in excess of normal.

Iron overload can also occur as a complication of

- Other hematologic disorders (e.g., inherited and acquired anemias).
- Chronic transfusion therapy or repeated injections of iron dextram.
- Chronic hepatitis.
- Excessive iron ingestion.

Once iron is absorbed, there is no physiologic mechanism for excretion of excess iron from the body other than blood loss (i.e., pregnancy, menstruation or other bleeding). Iron is bound and transported in the body via transferrin and stored in ferritin molecules. All cells of the body contain ferritin.

When iron absorption exceeds the storage capacity of ferritin molecules, unbound iron may promote free-radical formation in cells, resulting in membrane lipid peroxidation and cellular injury.

Iron deposition occurs in many organs.

Hemochromatosis

Hemochromatosis is a disease that occurs as a result of significant iron overload.

- Hemochromatosis can have genetic and non-genetic causes.
- Excess iron accumulates in organs (particularly the liver, pancreas, heart), joints, and the pituitary gland.
- After several decades of increased iron absorption non-specific symptoms (i.e., fatigue, weakness, arthralgia) develop, followed by advanced conditions (i.e., arthritis, cirrhosis, liver cancer).

Hemochromatosis symptoms usually develop after decades of increased iron absorption.

- Symptoms usually appear after 15-20 g of iron have accumulated in the body.
- Men thus tend to become symptomatic in middle age (40s) and women who stop menstruating develop symptoms about 15 years later

HFE gene mutations

The *HFE* gene codes for a transmembrane glycoprotein that modulates iron uptake. This protein is highly expressed in intestinal cells at the site of dietary iron absorption.

Mutations in the *HFE* gene compromise its function and can lead to iron overloading.

- The precise mechanism by which the HFE protein is involved in normal iron metabolism is incompletely understood but is a topic of much research.
- Recent studies suggest that loss of a functional HFE protein leads to increased iron uptake in the intestinal epithelial cell, which results in increased dietary iron absorption. (Britton RS, 2002; Fleming RE, 2002; Philpott CC, 2002; Townsend A, 2002).

Hereditary hemochromatosis

Hereditary hemochromatosis is the genetic disease that results from significant iron overload.

- The majority of hereditary hemochromatosis (also known as Type 1 Hemochromatosis) is associated with homozygous mutations in the *HFE* gene.
- There are other heritable forms of hemochromatosis, some of which are caused by mutations in other known genes.

People with *HFE* mutations may have much greater iron stores because they absorb dietary iron at 2-3 times the normal rate absorbing a few extra milligrams of iron per day.

- This leads to the accumulation of 0.5-1.0 g of iron per year.

- Once absorbed, there is no physiologic mechanism for excretion of excess iron from the body other than blood loss (i.e., pregnancy, menstruation or other bleeding).
- Over decades this leads to iron overloading with total body iron stores that may exceed 50 g.

This online course focuses on adult onset *HFE* hereditary hemochromatosis.

Heritable and Acquired Disorders Associated with Iron Overload

Heritable Disorder	Cause of Iron Loading	Pattern of Inheritance
Hemochromatosis		
Hemochromatosis Type 1 (Adult)	*HFE* gene mutations	Autosomal recessive
Hemochromatosis Type 2A (Juvenile)	Unknown	Autosomal recessive
Hemochromatosis Type 2B (Juvenile)	*Hepcidin* gene mutations	Autosomal recessive
Hemochromatosis Type 3	Transferrin receptor 2 inactivation	Autosomal recessive
Hemochromatosis Type 4	*Ferroportin* gene mutations	Autosomal dominant
Hemochromatosis Type 5 (Japanese Iron Overload)	*H-ferritin* gene mutation	Autosomal dominant
Other heritable disorders		
Porphyria cutanea tarda	Heterogeneous	Autosomal dominant or sporadic
African iron overload	Unknown	Autosomal dominant
Neonatal iron overload	In-utero iron transfer	Heterogeneous
Atransferrinemia	*Transferrin* gene mutations and red cell transfusions	Autosomal recessive
Aceruloplasminemia	*Ceruloplasmin* gene mutations	Autosomal recessive
Hereditary hyperferritinemia cataract syndrome	*L-ferritin* gene mutations	Autosomal dominant
Friedreich ataxia	*Frataxin* gene mutations	Autosomal recessive
B-Thalassemia major	*B-globin* gene mutations, chronic hemolysis, red cell transfusions	Autosomal recessive
Hereditary X-linked sideroblastic anemia	*d-ALA synthase* gene mutations	X-linked
Pyruvate kinase deficiency	*Pyruvate kinase* gene mutations	Autosomal recessive
G6PD deficiency	*G6PD* gene mutation	X-linked
Congenital dyserythropoeitic anemia Type I	Ineffective erythropoeisis	Autosomal recessive
Congenital dyserythropoeitic anemia Type II	Ineffective erythropoeisis	Autosomal recessive
Congenital dyserythropoeitic anemia Type III	Ineffective erythropoeisis	Autosomal dominant

Pantothenate Kinase-Associated Neurodegeneration	*Pantothenate kinase 2* gene mutations	Autosomal recessive
Acquired disorders		
Transfusions	Red cell iron transfusion	
Medicinal iron	Excessive iron ingestion	
Myelodysplasia with ring sideroblasts	Excessive iron absorption	
Portocaval shunt	Excessive iron absorption	

(Adapted from: Edwards CQ. Hemochromatosis. In: Wintrobe's Clinical Hematology,11th ed., chapter 30. Lippincott, Williams, and Wilkens, in press, 2003)

Summary of pathophysiology module

Iron overload

- Iron overload is the accumulation of excess iron in body tissues.
- Once iron is absorbed, there is no physiologic mechanism for excretion of excess iron from the body other than blood loss (i.e., pregnancy, menstruation or other bleeding).
- Iron is bound and transported in the body via transferrin and stored in ferritin molecules.
- The liver and heart are especially vulnerable.

Hemochromatosis

- Hemochromatosis is a disease that occurs as a result of significant iron overload. It can have genetic (majority of cases) or non-genetic causes.
- Men tend to become symptomatic in middle age (40s) and women who stop menstruating develop symptoms about 15 years later.

***HFE* gene mutations**

- *HFE* gene mutations can lead to iron overloading.

Hereditary hemochromatosis

- Hereditary hemochromatosis is the genetic disease that results from significant iron overload.
- The majority of hereditary hemochromatosis (also known as Type 1 Hemochromatosis) is associated with homozygous mutations in the *HFE* gene.
- People with *HFE* mutations absorb a few extra milligrams of iron per day. Over decades, this leads to iron overloading that can lead to disease.

Test your knowledge

This is an optional self-quiz and is not required for continuing education credit. Select the best answers below. If you need help, feel free to go back to Iron Overload and review.
(Check the best answer)

Question 1: An accumulation of excess iron in body tissues as a result of a genetic predisposition or complication of a hematological disorder is

a. Iron overload
b. Hemochromatosis
c. Hereditary hemochromatosis

Answer question 1:

(a). Correct

Iron overload refers to an accumulation of excess iron in body tissues as a result of a genetic predisposition to absorb excess iron or as a complication of other disorders.

(b). Incorrect

Iron overload refers to an accumulation of excess iron in body tissues; hemochromatosis is a disease that occurs as a result of significant iron overload.

(c). Incorrect

Iron overload refers to an accumulation of excess iron in body tissues; hereditary hemochromatosis is a genetic disease that results from significant iron overload.

Question 2: A genetic disease that results from significant accumulation of excess iron in body tissues is

a. Iron overload
b. Hemochromatosis
c. Hereditary hemochromatosis

Answer question 2:

(a). Incorrect

Incorrect. Iron overload is an accumulation of excess iron in body tissues as a result of a genetic predisposition or complication of a hematological disorder.

(b). Incorrect

Hemochromatosis is a disease that occurs as a result of significant iron overload and can have genetic and non-genetic causes.

(c). Correct

The majority of hereditary hemochromatosis is associated with homozygous mutations in the *HFE* gene. Other heritable forms are presumably associated with other genes.

Hereditary hemochromatosis = iron overload + disease + *HFE* gene mutations.

Question 3: A disease that occurs as a result of a significant accumulation of excess iron in body tissues and can have genetic and non-genetic causes is

a. Iron overload
b. Hemochromatosis
c. Hereditary hemochromatosis

Answer question 3:

(a). Incorrect

Iron overload refers to an accumulation of excess iron in body tissues as a result of a genetic predisposition to absorb excess iron or as a complication of other disorders.

(b). Correct.

Excess iron accumulates in vulnerable tissues and over time this overloading can result in hemochromatosis. Hemochromatosis can have genetic and non-genetic causes.

Hemochromatosis = iron overload + disease

(c). Incorrect

Hereditary hemochromatosis is a genetic disease resulting from significant iron overload.

Question 4: *HFE* gene mutations

a. Lead to calcium deficiency.
b. Usually lead to decreased absorption of dietary iron.
c. Can lead to iron overloading and the development of clinical signs and symptoms of hemochromatosis.

Answer question 4:

(a). Incorrect

HFE gene mutations do not lead to calcium deficiency.

(b). Incorrect

HFE gene mutations usually lead to **increased** absorption of dietary iron.

(c). Correct

HFE gene mutations **can lead to** development of clinical signs and symptoms consistent with hereditary hemochromatosis.

EPIDEMIOLOGY MODULE

Early detection of iron overload requires an understanding of the complex relationships between prevalence of iron overload, *HFE* gene mutations and penetrance of the disease.

> "An important challenge for genomics and public health in the next decade is to develop the road map for integrating genetics into disease prevention and health promotion programs. Ultimately people die from diseases and not from genes. We need information, information, and more information! We need to collect, analyze, and disseminate population-level information on the prevalence of gene variants, disease burden, and gene-environment interaction. We also need to evaluate genetic tests and the utility of genetic information. The ultimate challenge is to determine the benefits of using genetic information to target interventions that improve health and prevent disease. The obvious issues are why, how, and when we should change our traditional public health-oriented interventions to become more targeted on the basis of individual differential susceptibilities to disease."
>
> Muin J. Khoury, MD, PhD
> Centers for Disease Control and Prevention
> Director, Office of Genomics and Disease Prevention

Content in this module includes

- Prevalence of iron overload and *HFE* gene mutations.
- Patients at risk for iron overload, hemochromatosis, and hereditary hemochromatosis.
- Penetrance of *HFE* gene mutations.
- Population screening.
- Understanding iron overload in the context of the patient's family and medical history.
- Evaluating iron overload in the context of the patient's medical and family history.

Prevalence

Iron overloading, as measured by a random (non-fasting) elevated transferrin saturation (TS) value, is estimated to occur in 1 to 6 people per 100 in the United States.

- A lower percentage of people who initially have a random elevated TS also have a persistently elevated TS: estimates range from 35% to 50%.
    - An even lower percentage of people who have persistently elevated TS measures also have an elevated serum ferritin (SF) value.
        - Thus, the proportion of people who will develop clinical signs and symptoms of hemochromatosis is even lower than the proportion of people with elevated SF values.

The wide range of prevalence estimates in the medical literature reflect laboratory cutoff values used to define elevated transferrin saturation and serum ferritin values (i.e., cutoff or abnormal levels), as well as differences in the study populations.

HFE genotypes

Hemochromatosis occurs as a result of significant iron overload; in the United States this usually occurs as a result of *HFE* gene mutations and is therefore called hereditary hemochromatosis. This course focuses on adult onset *HFE* hereditary hemochromatosis.

The *HFE* gene mutation was discovered in 1996 (Feder JN). Two mutations on the *HFE* gene, C282Y and H63D, account for the majority of hereditary hemochromatosis cases in the United States (Steinberg KK, 2001).

- Hereditary hemochromatosis is inherited in an autosomal recessive pattern.
- The C282Y/C282Y homozygous genotype accounts for the majority of cases (Hanson EH, 2001).
- Other mutations have been described but their clinical significance is unknown.
- *HFE* gene mutations account for the majority of cases, but only a small proportion of individuals who inherit these mutations develop clinical disease.

Possible types of *HFE* gene mutations

After two decades of intensive research, the genetic complexity of hereditary hemochromatosis is still unfolding. The majority of hereditary hemochromatosis cases are due to C282Y homozygosity.

C282Y

- The C282Y mutation, caused by a guanine to adenine transition at nucleotide 845 (TGC ⟶ TAC), results in the substitution of cysteine (C) by tyrosine (Y) at amino acid position 282 in the HFE protein product.
- The C282Y mutation alters HFE protein structure, disrupting its transport to and presentation on the cell surface.

H63D

- The H63D mutation results in the substitution of histidine (H) by aspartate (D) at amino acid position 63 in the HFE protein.
- The H63D mutation does not appear to prevent cell-surface expression, indicating that the C282Y mutation causes a greater loss of protein function than does H63D.

Other *HFE* gene mutations

- In addition to C282Y and H63D, more than 10 other missense mutations that cause amino acid substitutions have been documented. A missense mutation indicates a change in DNA, resulting in an amino acid substitution.
- In one, a substitution of cysteine (C) by serine (S) at amino acid position 65 (S65C) is implicated in a very mild form of hereditary hemochromatosis in rare instances.
- Other mutations have been described in *HFE* but most are very low frequency.

- There may be *HFE* gene mutations that have yet to be identified, or mutations in other iron-regulating genes that have not been determined. Because of this, having **a negative genetic test does not rule out potential significant iron overload.**

Note: Amino acid substitutions are given with the standard single-letter notation for amino acids: (tyrosine-Y, cysteine-C, histidine-H, aspartate-D)**.** (Umek RM, 2001).

(Bomford A, 2002; Mura C, 1999; Pointon JJ, Wallace D, 2000; Wallace DF, 2002; Waheed A, 1999)

HFE genotype frequencies

The population prevalence of the *HFE* mutations depends on race and ethnicity but is most prevalent among persons of European origin and descent.

- *HFE* gene mutations are found in a small but significant proportion of the general population.
- Published estimates of *HFE* genotype frequencies vary depending on how studies were performed and on the racial/ethnic distribution of the populations tested.

Frequencies of *HFE* genotypes in the general population and among hemochromatosis patients?

- **General population.**

  A recent review of published *HFE* genotype frequencies that focused on non-Hispanic North American Caucasians reported that about 9% of tested individuals are carriers of the C282Y mutation and about 0.5% are C282Y homozygotes (Hanson EH, 2001).

  A large cross-sectional population-based study of DNA samples from the Third National Health and Nutrition Examination Survey estimated the overall C282Y homozygote prevalence to be about 0.3% in non-Hispanic Caucasians, 0.06% in non-Hispanic blacks, and 0.03% in Mexican Americans (Steinberg KK, 2001).

  Although it is rare to find *HFE* mutations in African Americans who have iron overload (McNamara L, 1998), these mutations have been found in a few individuals (Barton JC, 2000 and 2001). It has been suggested that their appearance is due to admixture. Current research suggests that genes other than *HFE* are responsible for the majority of iron overload in African and Mexican Americans.

- **Among hemochromatosis patients.**

  A pooled analysis of major *HFE* prevalence studies among diagnosed hemochromatosis patients estimated that about 75% have the C282Y/C282Y genotype. A range of other *HFE* genotypes was found in the remaining cases, including C282Y/H63D (~5.0%) and H63D/H63D (~1.5%); some cases carried a single *HFE* mutation or no *HFE* mutations.

This finding suggests that non-genetic influences, additional *HFE* mutations, or variations in additional or modifying genes that affect iron metabolism may also lead to hemochromatosis (Hanson EH, 2001).

Penetrance

Penetrance is the proportion of individuals with specific genotypes who develop clinical disease.

Most prevalence estimates are based on the homozygous major mutation (C282Y/C282Y). Because clinical signs and symptoms used to define hereditary hemochromatosis differ among studies, penetrance estimates vary.

Early studies that used both self-reported symptoms and clinical signs to define hemochromatosis, reported clinical penetrance estimates ranging from 40 to 70% (Bradley LA, 1996).

More recent studies that used clinical signs or objective laboratory measures to define hemochromatosis, reported clinical penetrance estimates ranging from <1 to 50% (Asberg A, 2001; Beutler E, 2002; Bulaj ZJ, 2000; Olynyk JK, 1999).

Inconsistencies regarding penetrance estimates persist in the scientific literature. Further studies are warranted to more fully understand the role of genetic and environmental factors that may affect penetrance.

Of people with *HFE* mutations, only a subset will develop elevated TS values. Of those with an elevated TS, only a subset will develop an elevated SF. Of those with an elevated SF, only a subset will develop hemochromatosis symptoms. Of those with symptoms, only a subset will develop clinical signs consistent with hemochromatosis.

Most clinicians reserve the hemochromatosis diagnosis for patients whose signs and symptoms are clearly referable to documented iron overload.

Iron status testing is more clinically relevant than genetic testing for identifying those who have hemochromatosis.

Population screening

Some experts advocate population screening for *HFE* mutations. In fact, it has been suggested that hereditary hemochromatosis serve as a model for formulating policy decisions about genetic diseases, in particular for decisions about the usefulness of genetic screening.

- Of utmost concern is the uncertainty about what proportion of people with *HFE* gene mutations will develop hemochromatosis.
- Current research suggests that penetrance may be low making population screening inefficient.

Therefore, CDC does not currently recommend population screening for *HFE* mutations.

However, genetic testing for *HFE* mutations can be useful to determine a specific cause for iron overload. In addition, in families with known hereditary hemochromatosis, genetic testing can determine which family members do not have *HFE* gene mutations.

Summary of epidemiology module

Prevalence

- Reported U.S. population prevalence estimates of iron overloading (based on random non-fasting elevated transferrin saturation [TS] values) range from 1% to 6%.
- A lower percentage of people who initially have a random elevated TS also have persistently elevated TS: estimates range from 35% to 50%.
- An even lower percentage of people with persistently elevated TS measures also have elevated serum ferritin values.
- Thus, the proportion of people who will develop clinical signs and symptoms of hemochromatosis is even lower than the proportion of people with elevated serum ferritin (SF) values.

HFE gene mutations

- Two *HFE* gene mutations, C282Y and H63D, account for the majority of hereditary hemochromatosis cases; C282Y is most common.
- Hereditary hemochromatosis is inherited in an autosomal recessive pattern.

HFE genotype frequencies

- The population prevalence of *HFE* mutations depends on race and ethnicity but is most prevalent among persons of European origin and descent.

Penetrance

- Of people with *HFE* gene mutations, only a subset will develop an elevated TS. Of those with an elevated TS, only a subset will develop an elevated SF. Of those with an elevated SF, only a subset will develop hemochromatosis symptoms. Of those with symptoms, only a subset will develop clinical signs consistent with hemochromatosis.
- Most clinicians reserve the hemochromatosis diagnosis for patients whose signs and symptoms are clearly referable to documented iron overload as reflected by serum iron testing measurements.
- Iron status testing is more clinically relevant than genetic testing for identifying those who have hemochromatosis.

Population screening

- At this time, CDC does not recommend population screening for *HFE* gene mutations because of the uncertainty about what proportion of people with *HFE* gene mutations will develop hemochromatosis.

Test your knowledge

This is an optional self-quiz and is not required for continuing education credit.Select the best answers below. If you need help, feel free to review.
(Check all that apply)

Question 1: Which of the following factors may place a patient at increased risk of developing hemochromatosis?

- ☐ European origin and descent.
- ☐ Blood relative with documented iron overload.
- ☐ Blood relative with a documented *HFE* gene mutation.
- ☐ Blood relative with documented hemochromatosis.
- ☐ Blood relative with documented hereditary hemochromatosis.

Answer question 1:

All of these factors may place a patient at increased risk of developing hemochromatosis.

A patient of European origin and descent may be at risk.
A patient may be at risk if he/she has a blood relative with documented:

- Iron overload.
- *HFE* gene mutation.
- Hemochromatosis.
- Hereditary hemochromatosis.

Question 2: True/False
Of people with *HFE* gene mutations, only a subset will develop clinical signs consistent with hemochromatosis.

a. True
b. False

Answer question 2:

(a). Correct.

Of people with *HFE* gene mutations, only a subset will develop clinical signs consistent with hemochromatosis.

(b). Incorrect.

The statement is true. Of people with *HFE* mutations, only a subset will develop an elevated TS. Of those with an elevated TS, only a subset will develop an elevated SF. Of those with an elevated SF, only a subset will develop hemochromatosis symptoms. Of those with symptoms, only a subset will develop clinical signs consistent with hemochromatosis.

CLINICAL FEATURES MODULE

There are no symptoms specific to hemochromatosis. A hemochromatosis diagnosis can be missed even in advanced stages unless looked for specifically (Hanson EH, 2001).

> "When hereditary hemochromatosis was considered a very rare disease and diagnosis relied on severe signs, such as the triad of cirrhosis, diabetes mellitus, and skin bronzing, along with evidence of iron overload on tissue biopsy, there was little controversy about its diagnosis. Now, however, the recognition that these severe disease manifestations are preventable with early treatment has led to strong interest in early diagnosis of the disease."
>
> Wylie M. Burke, PhD, MD
> Professor and Chair, Department of Medical History and Ethics, Universjty of Washington

Health care professionals can facilitate early diagnosis by maintaining a high index of suspicion for patients who have early signs or symptoms of this disease.

Content in this module includes

- Factors that may contribute to the clinical expression of hemochromatosis.
- Early stages of hemochromatosis.
- Advanced stages of hemochromatosis.

Clinical expression

Many factors contribute to the clinical expression of hemochromatosis:

- Rate of iron absorption.
- Age. The majority of cases are recognized in midlife, when body iron stores have accumulated.
- Gender. Onset in males is usually earlier than in females, who may be at lower risk due to pregnancies and menstrual blood losses.
- Dietary influences.
    - Iron supplements can accelerate iron accumulation.
    - Alcohol contributes to cirrhosis of the liver.
    - Vitamin C increases iron absorption.
- Iron losses. Loss of iron from other processes (blood donation, menstruation, occult bleeding, pregnancy) may delay onset.
- Presence of other diseases or toxins.
- Modifier genes.

The iron accumulation rate and the frequency and severity of clinical symptoms vary widely. Most patients may have no early symptoms. Little is known about the time from iron loading onset to development of symptoms or injury to body organs.

Early stages of hemochromatosis

Hemochromatosis symptoms are non-specific and seldom by themselves suggest a hemochromatosis diagnosis.

The most commonly associated early hemochromatosis symptoms may include:

- Fatigue.
- Weakness.
- Weight loss.
- Abdominal pain.
- Arthralgia.

If a patient presents with non-specific symptoms and uncertain etiology, consider a hemochromatosis workup.

As iron accumulation progresses, patients may also experience:

- Arthritis.
- Symptoms of gonadal failure.
    - For example, amenorrhea, early menopause, loss of libido, impotence.
- Shortness of breath/dyspnea.

Advanced stages of hemochromatosis

Iron accumulates in the parenchymal cells of several organs; the liver is a major site, followed by the heart and pancreas.

Conditions associated with advanced stages of hemochromatosis include:

- Arthritis.
- Abnormal liver function (e.g., elevated transaminase and clinical liver disease).
- Glucose intolerance and diabetes.
- Chronic abdominal pain.
- Severe fatigue.
- Hypopituitarism.
- Hypogonadism.
- Cardiomyopathy and arrhythmia.
- Cirrhosis.
- Liver cancer.
- Heart failure.
- Gray or bronze skin pigmentation.

Primary disorders associated with advanced hemochromatosis

Most advanced hemochromatosis complications are also common primary disorders. A hemochromatosis diagnosis can be missed even in advanced stages unless looked for specifically (Hanson EH, 2001). Some complications are not clearly related to excess iron, yet, when excess iron is removed, many patients report feeling better.

The liver is usually the first affected organ. Hepatomegaly is one of the most frequent findings at clinical presentation, followed by cirrhosis. Primary

hepatocellular carcinoma is more common in hemochromatosis patients with cirrhosis than in the general population (Haddow JE, 2003; Niederau C, 1985; Willis G, 2000).

Diabetes mellitus occurs in 25%–75% of patients. It is more likely to develop in those with family histories of diabetes, suggesting that direct damage to pancreatic islets by iron deposition occurs in combination with a genetic predisposition.

Arthropathy develops in 25%-50% of patients. It usually occurs after age 50, but may occur as a first manifestation or long after therapy.

Cardiac involvement is the presenting manifestation in about 15% of patients. The most common manifestation is palpitations as symptoms of arrhythmia.

Hypogonadism occurs in both sexes and may antedate other clinical features. Manifestations include loss of libido, impotence, amenorrhea, testicular atrophy, gynecomastia, and sparse body hair.

Excessive skin pigmentation is present in more than 90% of symptomatic patients at diagnosis.

Note: See Barton JC (1998) for more in depth information about the clinical stages of hemochromatosis.

Summary of clinical features module

Clinical expression

- The iron accumulation rate and the frequency and severity of clinical symptoms vary widely and may be dependent on factors such as age, gender, and diet.

Early stages

- The most commonly associated early hemochromatosis symptoms are non-specific and may include:
    - Fatigue.
    - Weakness.
    - Weight loss.
    - Abdominal pain.
    - Arthralgia.
- As iron accumulation progresses, patients may also experience:
    - Arthritis.
    - Symptoms of gonadal failure.
        - For example, amenorrhea, early menopause, loss of libido, impotence.
    - Shortness of breath/dyspnea.
- Maintain a high index of suspicion of hemochromatosis for patients with early signs or symptoms of this disease.

Advanced stages

- Iron accumulates in the parenchymal cells of several organs; the liver is a major site followed by the heart and pancreas.
- The liver is usually the first organ to be affected, but signs of organ damage occur in the later stages of the disease.

Primary disorders associated with advanced hemochromatosis

- Most advanced hemochromatosis complications are also common primary disorders.
- A hemochromatosis diagnosis can be missed even in advanced stages unless looked for specifically.

Test your knowledge

This is an optional self-quiz and is not required for continuing education credit. Select the best answers below. If you need help, feel free to review.

(Check all that apply)

Question 1: Which of the following patient presentations might prompt you to consider hemochromatosis?

☐ An older thin person with recent onset of diabetes and no family history of diabetes.
☐ A young person with pain in the second and third metacarpal joints.
☐ A middle-aged person with non-specific symptoms such as fatigue, arthralgia, or weakness who has had numerous office visits.

Answer question 1:

Your index of suspicion should be raised with all of these patient presentations.

Question 2: As iron accumulation progresses, patients may experience loss of libido and impotence.

a. True.
b. False.

Answer question 4:

(a). Correct

As iron accumulation progresses, patients may experience symptoms of gonadal failure such as loss of libido, impotence, amenorrhea, and early menopause.

(b). Incorrect

As iron accumulation progresses, patients may experience symptoms of gonadal failure such as loss of libido, impotence, amenorrhea, and early menopause.

DIAGNOSTIC TESTING MODULE

Evaluating the iron status of patients with these vague, non-specific symptoms facilitates identifying patients early in the disease rather than later when symptoms have already developed.

> "In our physician study, 23% were unaware of the population at risk for developing hemochromatosis. Education programs should emphasize that hemochromatosis is common, that elevated values of serum transferrin saturation can be used to diagnose most cases before iron overload occurs, and that phlebotomy to achieve and maintain normal body stores of iron is the preferred treatment."
>
> Ronald T. Acton, PhD
> Professor of Microbiology
> University of Alabama, Birmingham

Content in this module includes:

- Biochemical testing for iron status
- Ordering transferrin saturation and serum ferritin lab tests
- Interpreting lab tests results to evaluate iron status.
- Confirming a diagnosis of hemochromatosis.

Biochemical testing

Biochemical testing for iron status is recommended for patients with

- Symptoms or signs suggestive of hemochromatosis:
  - Severe weakness or fatigue.
  - Unexplained joint or abdominal pain.
  - Signs of liver disease, diabetes, or heart problems.
  - Impotence, infertility, and loss of menstrual periods.
- Porphyria, hepatitis, or other liver diseases.
- Abnormal blood tests consistent with hemochromatosis:
  - Elevated transferrin saturation,
  - Elevated serum ferritin,
  - Elevated transaminase (indicative of liver disease).
  - Elevated blood glucose (indicative of diabetes).

Evaluation for other causes of these medical problems should also be performed.

Biochemical testing for iron status is also recommended for family members of diagnosed hemochromatosis patients.

  - These individuals have an increased risk of developing iron overload and are an ideal group for targeted prevention efforts.

Biochemical tests for assessing iron overloading

The simpliest tests that indirectly indicate iron overloading are serum iron and iron-binding capacity, which allows calculation of percent transferrin saturation.

Serum ferritin correlates well with iron stores but its normal value rises with age and varies with gender; it can also be elevated with liver disease, inflammation, and neoplasm.

Biochemical tests include

- Serum iron (SI).
- Total iron-binding capacity (TIBC).
- Unsaturated iron-binding capacity (UIBC).
- Transferrin saturation (TS).*****
- Serum ferritin (SF).

Note:* TS is sometimes called iron saturation because the majority of laboratories use a surrogate TS marker instead of measuring transferrin levels. These surrogate measures are serum iron and iron-binding capacity (total iron-binding capacity [TIBC] or unbound iron-binding capacity [UIBC]). Measuring transferrin for TS requires immunologic measurement, a procedure that is costly and too time-consuming for most clinical laboratories.

Recommended laboratory tests for the workup of a patient you suspect may have hemochromatosis are

- **Fasting transferrin saturation test (TS)**
  - SI and either TIBC or UIBC are usually used to calculate TS.
  - TS = (SI/TIBC X 100)
  - TS = (SI/SI + UIBC X 100)
- **Serum ferritin test (SF)**

Note: Due to patient compliance issues, a TS value obtained from a nonfasting blood draw can be used to screen a patient for iron overload. Non-fasting TS values greater than 60% indicate iron overload. Non-fasting TS values between 45% and 60% are considered evidence of borderline elevation. A repeat TS from a fasting blood draw should then be obtained.

Ordering a transferrin saturation test

In February 1997, a panel of medical experts convened by the CDC recommended that transferrin saturation (TS) be used as the initial diagnostic test for hereditary hemochromatosis.

The most frequently used method for determining TS requires an assay of serum iron and the total iron-binding capacity (TIBC) of serum proteins.

Serum iron is a measure of circulating iron bound to transferrin and reflects total body iron. Because serum iron measurements may be affected by menstrual cycle, time of day, diet, hepatitis, and use of iron containing placebos found in some oral contraceptive packages, serum iron levels alone are not sensitive indicators of iron status.

The major iron-binding and transport protein in serum is transferrin, although small amounts of iron may be bound to ferritin, albumin, and other proteins or compounds.

Transferrin levels, along with serum iron levels as part of the TIBC test, are useful in the differential diagnosis of many disorders, including hemochromatosis (Witte DL, 1996).

Transferrin saturation (TS) can be determined by two common methods:

1. Measurement of TIBC. TS = (serum iron/TIBC x 100).

2. Sum of measured unsaturated iron-binding capacity (UIBC) and measured serum iron.
TS = (serum iron/ [serum iron + UIBC] x 100).

Note: Few laboratory order forms will have TS category lines. Ordering serum iron and a TIBC will allow for the calculation of TS. If TIBC is not an option, order serum iron and UIBC.

Testing protocol

Step 1: Transferrin saturation test.
Step 2: Serum ferritin test.
Step 3: Confirmation.
a. Indirectly by quantitative phlebotomy
b. *HFE* genotyping
c. Directly by liver biopsy

Step 1: Transferrin saturation test.

The transferrin saturation test (TS) is a sensitive and relatively inexpensive biochemical measure of iron overloading.

Transferrin is a blood protein that picks up iron absorbed by the intestines and transports it from one location to another. When iron absorption is abnormally high, transferrin proteins become more saturated with iron. An elevated TS value therefore reflects an increase in iron absorption.

The first step in working up a patient with suspected iron overload is the TS measurement in a fasting blood draw.

Interpreting the results of a fasting transferrin saturation (TS) test:

Transferrin saturation (%)	Interpretation	Action
<16%	Low	Consider iron deficiency.
16%-45%	Normal	Reassure patient that he/she does not have iron overload, return to usual care. *
>45%	Elevated	Proceed with serum ferritin tests and additional workup as warranted.

(EASL, 2000; CDC Expert Panel on Hemochromatosis, 2000 and 2002).

When interpreting the results of a fasting transferrin saturation (TS) test, keep in mind that:

- Several factors can falsely elevate TS values, including the use of vitamin C, dietary supplements containing iron, medicinal iron, and estrogen preparations. Patients should be advised to avoid these products for 24 hours prior to the fasting blood draw. The placebos contained in some oral contraceptive packages may contain iron. These iron containing placebos should be avoided for 24 hours prior to the fasting blood draw.
- Colds, inflammation, liver disease, and malignancies can falsely lower TS values.
- Pathologic blood loss or a history of frequent blood donations should be considered reasons for normal iron status in patients who have symptoms consistent with hemochromatosis.

Note: Patients with nonalcoholic steatohepatitis can exhibit normal TS but may exhibit elevated SF.

Step 2: Serum ferritin test.

Patients with elevated TS values should proceed with serum ferritin testing and additional workup as warranted.

Ferritin is a protein that stores iron. The body increases serum ferritin production when excess iron is absorbed. Serum ferritin levels therefore reflect the body's iron stores.

Note: Because serum ferritin is also an acute phase reactant affected by cancer and inflammatory or infectious processes, SF values may increase if these underlying conditions are present.

Interpreting serum ferritin test results in patients with elevated fasting TS:

SF levels ng/mL	Interpretation	Action
<200 for premenopausal females **OR** <300 for males	Normal	Recheck every 2 years and reassure patient that he/she does not have iron overload.
200-300 for post-menopausal female	Borderline elevation	Consider other factors in making the recommendation to treat or observe.
>200 for premenopausal female **OR** >300 for postmenopausal female **OR** >300 for male	Elevated	In the absence of other causes, removal of iron via phlebotomy is indicated. Confirmation of hemochromatosis is warranted.

(EASL, 2000; Barton JC, 2000; CDC Expert Panel on Hemochromatosis, 2000, 2002).

Step 3: Confirming the hemochromatosis diagnosis.

Additional biochemical evidence of iron overload is typically required before the hemochromatosis diagnosis is made.

Confirmation can be achieved in three ways:

a. Indirectly by quantitative phlebotomy.

Most health care providers consider quantitative phlebotomy the confirmatory test of choice.

The amount of mobilizable iron removed from the body by weekly or biweekly phlebotomy is an accepted criterion for measuring the degree of iron overload and confirming a hemochromatosis diagnosis (EASL, 2000).

Removal of 3 g or more of mobilizable iron stores before the development of iron-limited erythropoiesis confirms the presence of primary iron overload due to hemochromatosis.

This typically requires approximately 15 phlebotomies, each removing 500 mL of blood. Each 500 mL of blood extracted removes approximately 200 mg of iron. The goal is to reduce the ferritin level to ~ 20 ng/mL.

b. *HFE* genotyping.

Genotyping for *HFE* mutations can provide additional confirmatory evidence that a patient has hereditary hemochromatosis.

However, this information should be combined with clinical history, examination, and laboratory assessment.

Identification of any *HFE* mutation is, by itself, insufficient for diagnosing hereditary hemochromatosis (EASL, 2000). Other heritable forms of hemochromatosis may not be part of the standard genetic screen because some *HFE* mutations are not yet identified. Other genes involved in iron metabolism may be responsible for iron overloading (EASL, 2000; Pietrangelo A, 1999).

Therefore, if a patient is negative for an *HFE* mutation yet has disease symptoms and iron overload, phlebotomy treatment and proper management of the patient's iron overload are still important.

c. Directly by liver biopsy.

Liver biopsy directly assesses the amount of iron per gram of liver tissue.

Many authorities once considered liver biopsy an essential diagnostic test when hemochromatosis was suspected because of clinical or biochemical abnormalities.

Today, liver biopsy is used more often as a prognostic, rather than a diagnostic, test (Whittington CA, 2002; Barton JC, 1998).

- A recent study by Morrison ED et al. (2003) concluded patients with hemochromatosis and serum ferritin levels less than 1000 ng/mL are unlikely to have cirrhosis.
    - Liver biopsy may be unnecessary to determine fibrosis or cirrhosis in patients with serum ferritin level less than 1000 ng/mL, normal serum AST and ALT levels, and without excess alcohol intake or risk factors for other liver disease.
    - Conversely, the authors suggest liver biopsy be considered for patients with serum ferritin levels greater than 1000 ng/mL because of significantly increased risk for advanced fibrosis.

Summary of diagnostic testing module

Biochemical testing

- Biochemical testing for iron status is recommended for patients with
    - Symptoms or signs suggestive of hemochromatosis.
    - Porphyria, hepatitis or other liver diseases.
    - Abnormal blood tests consistent with hemochromatosis.
- Evaluation for other causes of these medical problems should also be performed.
- Testing is also recommended for family members of diagnosed patients.
- Recommended laboratory iron tests for the workup of a patient you suspect may have hemochromatosis are
    - Fasting transferrin saturation test (TS).
    - Serum ferritin test (SF).

Testing protocol

- Transferrin saturation (TS).
    - Fasting values >45% should be followed by a serum ferritin test and additional workup.
- Serum ferritin (SF).
    - Values >200 ng/mL for premenopausal females OR >300 ng/mL for postmenopausal females and males indicate iron overload; phlebotomy treatment is warranted in the absence of other causes.
    - SF values can be elevated with liver disease, inflammation, and neoplasm.
- Confirmation of iron overload is typically required:
    - Most health care providers consider quantitative phlebotomy the confirmatory test of choice.
    - Genotyping for *HFE* mutations can provide additional confirmatory evidence that a patient has hereditary hemochromatosis.
    - Many authorities once considered liver biopsy an essential diagnostic test, but it is now used more often as a prognostic, rather than a diagnostic, test.

Test your knowledge

This is an optional self-quiz and is not required for continuing education credit. Select the best answers below. If you need help, feel free to review.

(Check all that apply)

Question 1: Biochemical testing for iron overload is recommended for:

☐ Patients with vague, unexplained non-specific symptoms of hemochromatosis.
☐ Patients with hepatitis.
☐ Family members (blood relatives) of patients diagnosed with iron overload.

Answer question 1:
Biochemical testing for serum iron status is recommended for:

- Patients with symptoms or signs suggestive of hemochromatosis.
- Patients with porphyria, hepatitis or other liver diseases.
- Family members (blood relatives) of patients diagnosed with iron overload..

(Click on the best answer)

Question 2: Fasting serum iron levels and _____are used together as a marker of transferrin saturation (TS).

a. Serum ferritin.
b. Iron-binding capacity (TIBC or UIBC).
c. Transaminase.

Answer question 2:

(a). Incorrect.

Serum iron and TIBC or UIBC are used to calculate transferrin saturation. These are the simplest tests that indirectly indicate iron status and are the first diagnostic tests ordered.

(b). Correct.

Serum iron and TIBC or UIBC are used to calculate transferrin saturation. These are the simplest tests that indirectly indicate iron status and are the first diagnostic tests ordered.

(c) Incorrect.

Serum iron and TIBC or UIBC are used to calculate transferrin saturation. These are the simplest tests that indirectly indicate iron status and are the first diagnostic tests ordered.

Question 3: The diagnostic test of choice to confirm hemochromatosis is _____.

a. Liver biopsy.

b. *HFE* genotyping.
c. Quantitative phlebotomy.

Answer question 3:

(a). Incorrect

Liver biopsy is used as a prognostic indicator rather than a diagnostic test.

(b). Incorrect

A patient who is negative for *HFE* gene mutations yet has disease symptoms and iron overload still requires quantitative phlebotomy to confirm hemochromatosis. A limitation of genotyping is that mutations not yet identified may prove to be responsible for iron overloading.

(c). Correct

Quantitative phlebotomy is the diagnostic test of choice to confirm hemochromatosis.

TREATMENT & MANAGEMENT MODULE

Early detection of iron overload and hemochromatosis treatment can delay or prevent irreversible complications and prolong life. Phlebotomy, the treatment of choice, is relatively easy, safe, and inexpensive.

> "While scientists struggle to understand the molecular subtleties of hemochromatosis, the clinical treatment of the disorder remains remarkably primitive: serial phlebotomy. Removing about a pint of blood a week can prevent excess iron from accumulating, and if started early enough, can often reverse disease symptoms"
>
> David A. Shaywitz, MD, PhD
> Harvard Medical School
> Massachusetts General Hospital
> New York Times 2003

Content in this module includes

- Phlebotomy treatment and its benefits.
- Mechanisms of phlebotomy.
- Planning and monitoring the phlebotomy regimen.
- Compliance.
- Downloadable information for patients.

Phlebotomy treatment

Therapeutic phlebotomy is the preferred treatment for reducing iron stores in hemochromatosis patients.

If begun early in the course of iron loading, phlebotomy can prevent most iron overload complications.

- For a patient who has no evident tissue or organ damage, proper disease management may result in a normal long-term outcome and life expectancy.
- For a patient who has tissue or organ damage, further damage can be halted but damage already incurred may not be reversible.
- Even after the occurrence of complications, however, phlebotomy can decrease symptoms and improve life expectancy for patients with iron overload.

Expected benefits of phlebotomy treatment

At diagnosis**,** degree of organ damage is the major determinant of patient prognosis.

This table summarizes the expected benefits of treatment among hemochromatosis patients completing therapeutic phlebotomy treatment:

Pretreatment State	Expected Benefit
No symptoms	Prevention of complications of iron overload; normal life expectancy.
Weakness, fatigue, lethargy	Resolution or marked improvement if iron related.
Elevated serum concentrations of hepatic enzymes	Resolution or marked improvement.
Diarrhea	Cessation if iron related.
Hepatomegaly	Resolution often occurs.
Hepatic cirrhosis	No change or slower progression of liver failure.
Right-upper quadrant pain	Resolution or marked improvement.
Arthropathy	Some improvement in arthralgias, change in joint deformity; progression is sometimes seen.
Hypogonadotrophic hypogonadism	Resolution is rare.
Diabetes mellitus	Occasional improvement, if iron related.
Hyperthyroidism, hypothyroidism	Resolution is rare.
Cardiomyopathy	Resolution sometimes occurs.
Hyperpigmentation	Resolution usually occurs.
Hyperferritinemia	Resolution.
Hyperferremia	Little change to minor improvement.
Excess absorption and storage of nonferrous metals (cobalt, manganese, zinc, lead)	Little or no change.

Note: Increased risk for primary liver cancer can be reduced if the liver is precirrhotic.

(Barton JC, 1998 and 2000).

Physiologic mechanisms through which phlebotomy works

- As blood cells are extracted, bone marrow is stimulated to make new red blood cells (RBCs).
- Iron is transported from body stores to make hemoglobin, an integral part of the RBC. RBC production further increases to replace blood removed through phlebotomy.
- During treatment, iron stores are depleted for new RBC production and the patient's iron level is reduced to a safe and healthy level.

Normalization of iron stores typically involves the weekly removal of blood by phlebotomy until mild hypoferritinemia occurs (e.g., ferritin = 20 ng/mL on one occasion). Each unit (500 mL) of blood removed represents approximately 200 mg of iron.

Phlebotomy regimen

Clinicians must design phlebotomy treatment regimens that are individualized to each patient.

Patient factors to consider in designing the phlebotomy regimens include

- Age.
- Gender.
- Weight.
- General health.
- Likelihood of compliance.

Initial de-ironing phase

- Initial de-ironing usually takes from 3 months to 1 year.
- Volume of blood to be removed varies among patients.
    - Typically, 1 unit (500 mL) of blood is removed per week.
    - Patients with small body mass (i.e., women <110 lbs), elderly patients, and patients with anemia, cardiac problems, or pulmonary problems can often sustain removal of only 250 mL of blood per week.
- Initial iron depletion is complete when
    - the serum ferritin level is between 25 and 50 ng/mL,
    - the hemoglobin concentration is lower than 11.0 mg/dL, or
    - the hematocrit is lower than 0.33 for more than 3 weeks (in patients who do not have chronic anemia).

These values indicate that mild iron deficiency has been induced and potentially pathogenic iron deposits have been removed.

Monitoring treatment

Serum ferritin level is the most reliable, readily available, and inexpensive way to monitor therapeutic phlebotomy.

In general, patients who have higher serum ferritin levels have more severe iron overload and need more phlebotomies.

- Among patients who have serum ferritin levels greater than 1000 ng/mL before treatment, it is sufficient to measure the serum ferritin level every 4 to 8 weeks during the initial months of treatment.
- The serum ferritin levels should be measured more often in patients who have received multiple phlebotomy treatments and in those who have mild or moderate iron overload at diagnosis.
- Some experts also suggest checking hemoglobin values at each visit during treatment, while others suggest monitoring every 4-6 weeks. Normal hemoglobin levels range from 12-16 g/dL for females and 14-18g/dL for males (Merck Manual, 1999).

In all patients, serum ferritin levels should be quantified after each additional one or two treatments once the value is ≤100 ng/mL.

Clinical judgment and careful monitoring are essential to treatment.

Preventing abnormal iron reaccumulation

To prevent abnormal iron reaccumulation, serum ferritin levels should be monitored and additional phlebotomies scheduled as warranted.

- For the first year, determining how often phlebotomy should be performed is a matter of trial and error by physician and patient.

The table below depicts normal ranges and ideal maintenance for serum ferritin for men and women.

Serum Ferritin	Adult Males	Adult Females
Normal range	25-300 ng/mL	25-200 ng/mL
Ideal maintenance	25-50 ng/mL	25-50 ng/mL

(Barton JC, 1998 and 2000; CDC Expert Panel on Hemochromatosis, 2000 and 2002).

Lifetime maintenance

Continued lifetime monitoring is key to appropriate patient management. Phlebotomy should be performed throughout a patient's life to keep ferritin levels between 25 and 50 ng/mL.

This generally requires the annual removal of 3 or 4 units in men and 1 or 2 units of blood in women, on average.

- Some persons, especially elderly persons, may not require maintenance phlebotomies, but their serum ferritin levels should be monitored at least once a year (Barton JC, 2000).

At a minimum, yearly serum ferritin checks for continued maintenance of low body iron stores can prevent added hemochromatosis complications.

Potential problems associated with phlebotomy treatment

Careful monitoring of each patient throughout treatment is imperative. If treatment is too aggressive, anemia may result.

The logic of phlebotomy treatment is to induce mild temporary anemia and maintain it until iron storage is greatly reduced.

- When phlebotomy is too aggressive, however, red blood cell production is not sufficient to sustain healthy hemoglobin level, and forced anemia can result.
- Some physicians mistakenly use this initial state of anemia to signal that the patient is de-ironed and treatment can be suspended.

Younger patients can tolerate a temporary state of mild anemia but older patients may have difficulty with this approach to de-ironing. Extremely young or old patients, as well as those who are small and frail, may require an adjustment in the amount of blood removed.

After the initial de-ironing is accomplished, maintaining overt clinical anemia by phlebotomy is not justifiable. After iron depletion, the hemoglobin concentration and hematocrit should be allowed to return to and remain within the normal range (Barton JC, 1998).

Patients with hemoglobin concentrations lower than 11 mg/dL or hematocrits lower than 0.33 before treatment are more likely to have symptoms of hypovolemia and anemia; phlebotomy is less efficient at removing iron in these patients.

Many patients with chronic hemolytic anemia and iron overload, however, DO NOT tolerate phlebotomy well (Barton JC, 2000).

> **Notes:** Patients should be instructed to hydrate before and after a phlebotomy to prevent hypovolemia complications. Fluid intake of approximately 2 L per day is appropriate before and after the procedure. Patients should be observed for signs of hypovolemia (e.g., hypotension, tachycardia, increased respiratory rate, dizziness, weakness, change in mental status) during a phlebotomy and directly after.
>
> Elderly patients or patients with cardiac disease histories may require closer monitoring because they may more easily develop signs of hypovolemia. These patients also may need less blood removed at longer intervals (Wright SM, 2000).
>
> Additional monitoring considerations include hemoglobin concentration, hematocrit, and mean corpuscular volume.

Clinical judgment and careful monitoring are essential to treatment.

Chelation therapy

For patients who cannot be bled because of other heritable and acquired anemias, chelation therapy is an option.

- Iron chelation is the pharmacological removal of metals by chemicals that bind metal so that it is excreted in urine.
- The only pharmacological iron-chelating agent approved by the FDA for use in humans is intravenous deferoxamine, aka desferrioxamine, (DfO,Desferal*). This approach lacks the complete efficacy of phlebotomy and should be employed only when **absolutely** necessary.

* Desferal™ must never be used with compazine; the combination produces coma.

Iron chelation should not be confused with EDTA (ethylenediamine tetra-acetic acid) chelation.

- Claims for dietary supplements and other over-the-counter products that remove heavy metals may not have supporting data, especially for iron overload treatment.

When to refer: A primary care physician can manage hemochromatosis; however, if a patient has advanced disease, you may want to refer the patient to the appropriate specialist.

Where to refer: Contacts for therapeutic phlebotomy include

- Hospital blood banks.
- Community blood banks.
- Plasma centers.
- IV therapy centers.
- Local county medical society.

A hematologist may also be able to help identify phlebotomy sources.

Compliance

Patient compliance is crucial to successful treatment. Most patients tolerate phlebotomy treatment well.

For the majority of patients, compliance with phlebotomy treatment is related to the:

- Patient's understanding of the importance of lifetime treatment.
- Skill of the phlebotomist.
- Patient's confidence in the clinician.

Patient complaints related to phlebotomy treatment include:

- Fatigue as the most commonly reported problem.
- Discomfort or other problems from needle puncture.
- Tediousness of treatment.
- Concern that overbleeding may lead to anemia.
- Blood disposal as opposed to transfusion.

(EASL, 2000).

Encourage patients to:

- Drink fluids **before** and **after** treatment.
- Avoid vigorous physical activity for 24 hours after treatment.
- Continue phlebotomy treatments.

Download and print "Phlebotomy Information for Patients with Hemochromatosis".

Phlebotomy Information for Patients with Hemochromatosis

What is a phlebotomy (pronounced: flee-bot-o-me)?

It's the same procedure as when you donate blood. A nurse takes about a pint of blood from a vein in your arm. The procedure takes about an hour. A phlebotomy is simple, safe, and effective.

How often must I have a phlebotomy?

For about a year or more, you will probably have phlebotomies once or twice a week. How many phlebotomies you have and how often you have them depends on how much iron has built up in your body and what your doctor recommends.

Must I have phlebotomies for the rest of my life?

Yes. But after the iron is first lowered to a safe amount, you will have phlebotomies less often, usually a few times a year.

Does a phlebotomy have side effects?

Most people feel just fine. Others feel tired afterward and like to rest for an hour or so. It's a good idea to drink water, milk, or fruit juices before AND after a phlebotomy.

Where can I get a phlebotomy?

Therapeutic phlebotomy can be made in many places; including hospitals, clinics, and bloodmobiles (mobile blood drives on specially equipped buses). People can also donate at community blood centers and hospital-based donor centers. Many people donate at blood drives at their work places. Verify that the blood donation center can withdraw blood for your phlebotomy treatments at the frequency prescribed by your doctor. If you need help finding a blood donation center, check with your doctor.

The donation process

The donor lies down or sits in a reclining chair. The skin covering the inner part of the elbow joint is cleansed. A new, sterile needle that is connected to plastic tubing and a blood bag is inserted into an arm vein. The donor is asked to squeeze his or her hand repeatedly to help blood flow from the vein into the blood bag. Typically, one unit of blood, roughly equivalent to a pint, is collected. Collected blood is sent to the laboratory for testing. The donor is escorted to an observation area for light refreshments and a brief rest period.

Before treatment

- Drink water, milk, or fruit juice; liquids such as these will help increase blood flow and therefore shorten the amount of time a phlebotomy will take.

After Your Treatment

- Drink water, milk, or fruit juices after treatment.
- Avoid vigorous physical activity for 24 hours after treatment.
- Continue phlebotomy treatments as needed.

Without phlebotomies, iron overload may cause illness and premature death. Treatment is worth the effort.

Department of Health and Human Services
Centers for Disease Control and Prevention

Diet

Phlebotomy is the most simple, inexpensive, and effective treatment for hemochromatosis. There is no evidence that hemochromatosis can be treated by diet alone. However, many patients are concerned about their diet as an adjunct to phlebotomy.

Although studies are inconclusive about the dietary factors associated with high iron stores (Fleming DJ, 2002; Garry PJ, 2000), the following general diet modifications are suggested for hemochromatosis patients: (Barton JC, 2000; Expert Panel on Hemochromatosis, 2000 and 2002)

- **Avoid iron supplements.**
- Read the label of multivitamins to make sure they do not contain iron.
- Limit vitamin C supplementation to 500 mg/day. Vitamin C speeds up intestinal iron absorption. Eating natural foods that contain vitamin C is fine.
- Avoid eating raw shellfish. Hemochromatosis patients are susceptible to infections with *Vibrio vulnificus* and *Salmonella enteriditis*; raw shellfish can contain these bacteria.
- Avoid more than moderate alcohol consumption, one drink per day for females, no more than two per day for males. Patients with liver damage should avoid alcohol.

A dietitian who understands hemochromatosis can help formulate an effective diet plan if the patient has complex dietary requirements.

Compared to the importance of phlebotomy in managing iron overload, dietary factors probably play a minor role.

Download and print "Diet Information for Patients with Hemochromatosis".

Diet Information for Patients with Hemochromatosis

1. **Don't take iron pills**, nutritional supplements, or multivitamins with iron.

   - If you are taking a multivitamin, read the label to make sure it does not contain iron.

2. **Don't take pills with more than 500 mg of vitamin C** per day, vitamin C increases the amount of iron your body absorbs.

   - Eating foods that contain vitamin C is fine.

3. **Don't eat raw fish or raw shellfish.**

   - Cooking destroys germs that are harmful to people with iron overload, so it is okay to eat **well-cooked** fish and shellfish.

4. **Drink very little alcohol**, if you choose to drink.

   - Women should have less than one drink a day. Men should have less than two drinks a day.
   - If you have liver damage, do not drink alcohol.

5. **For more information** on iron and iron supplements, go to:

   - http://www.cc.nih.gov/ccc/supplements/iron.html
   - http://www.irondisorders.org

Hemochromatosis cannot be treated by diet alone.

Phlebotomy is important to the successful management of hemochromatosis.

Department of Health and Human Services
Centers for Disease Control and Prevention

Blood safety

Patients should be informed that blood collected during phlebotomy treatment is usually safe for transfusion and is an untapped resource for augmenting the U.S. blood shortage.

Myth: Blood from a patient with hemochromatosis or iron overload is iron rich.

Fact: One unit of blood contains about 200 mg iron, the same as blood from any other person. Excess iron is stored in an individual's organs, not in the blood supply.

Myth: Blood from a patient with hemochromatosis or iron overload is unsafe.

Fact: In 1999, the Food and Drug Administration (FDA) announced that blood from patients with hemochromatosis and iron overload (who pass the standard donation screening interview) is safe to use, but a blood donation facility must meet the following criteria: the blood collection center may not charge for therapeutic phlebotomy, and the blood center must apply to FDA for exemption from existing regulations. As part of that exemption, the blood center must collect and submit specified data to FDA. FDA will consider exemption applications case by case. The American Red Cross is currently studying their policies about accepting blood from hemochromatosis patients.

Patient questions about therapeutic phlebotomy and blood donations can be referred to the FDA and the Iron Disorders Institute.

Summary of treatment and management module

Phlebotomy treatment

- Therapeutic phlebotomy is the preferred treatment for reducing iron stores in hemochromatosis patients.
- For a patient who has no evident tissue or organ damage, proper disease management may result in normal long-term outcome and life expectancy.

Phlebotomy regimen

- Clinicians must design phlebotomy treatment regimens that are individualized to each patient and account for age, gender, weight, health, and likelihood of compliance.

Monitoring treatment

- Serum ferrinin levels should be measured after each additional one or two phlebotomy treatments once the value is ≤ 100 ng/mL.
- Careful monitoring of each patient throughout treatment is imperative. If treatment is too aggressive, anemia may result.

Lifetime maintenance

- Continued lifetime monitoring is key to appropriate management.
- Phlebotomy should be performed throughout a patient's life to keep the serum ferritin level between 25 and 50 ng/mL.

Compliance

- Download and print on your letterhead "Phlebotomy Information for Patients with Hemochromatosis".
- Hemochromatosis cannot be treated by diet alone.
- The following dietary modifications for patients are suggested:
    - Avoid iron supplements.
    - Read the label of multivitamins to make sure they do not contain iron.
    - Limit vitamin C supplementation to 500 mg/day.
    - Avoid eating raw shellfish.
    - Avoid more than moderate alcohol consumption. Patients with liver damage should avoid alcohol.
- Download and print on your letterhead "Diet Information for Patients with Hemochromatosis".

Test your knowledge

This is an optional self-quiz and is not required for continuing education credit. Select the best answers below. If you need help, feel free to review.

(Click the best answer)

Question 1: Which of the following can indicate that iron depletion is complete?

a. Hemoglobin concentration equals 14.0 mg/dL.
b. Hematocrit is lower than 0.50 for more than 2 weeks (in patients who don't have chronic anemia).
c. Serum ferritin level is between 25 and 50 ng/mL.

Answer question 1:

(a). Incorrect

Iron depletion is complete when the serum ferritin level is between 25 and 50 ng/mL or when the hemoglobin concentration is lower than 11.0 mg/dL or the hematocrit is lower than 0.33 for more than 3 weeks (in patients who don't have chronic anemia).

(b). Incorrect

Iron depletion is complete when the serum ferritin level is between 25 and 50 ng/mL or when the hemoglobin concentration is lower than 11.0 mg/dL or the hematocrit is lower than 0.33 for more than 3 weeks (in patients who don't have chronic anemia).

(c). Correct.

A serum ferritin level between 25 and 50 ng/mL indicates that mild iron deficiency has been induced and that potentially pathogenic iron deposits have been removed.

Question 2: Once iron depletion is complete, how often should serum ferritin be monitored to maintain low body iron stores?

a. At a minimum, yearly
b. At a minimum, every three years
c. At a minimum, every five years

Answer question 2:

(a). Correct

After the initial de-ironing is complete, at a minimum yearly serum ferritin checks to maintain low body iron stores can prevent additional hemochromatosis complications.

Clinical judgement should be used to determine if serum ferritin needs to be monitored more frequently in individual patients.

(b) Incorrect

After the initial de-ironing is complete, at a minimum yearly serum ferritin checks to maintain low body iron stores can prevent additional hemochromatosis complications.

Clinical judgement should be used to determine if serum ferritin needs to be monitored more frequently in individual patients.

(c) Incorrect

After the initial de-ironing is complete, at a minimum yearly serum ferritin checks to maintain low body iron stores can prevent additional hemochromatosis complications.

Clinical judgement should be used to determine if serum ferritin needs to be monitored more frequently in individual patients.

Question 3: Which of the following statements apply to patients undergoing phlebotomy treatments who have hemoglobin concentrations lower than 11 mg/dL or hematocrit lower than 0.33 before treatment?

a. Phlebotomy is more efficient at removing iron in these patients.
b. These patients are less likely to have symptoms of anemia.
c. These patients are more likely to have symptoms of hypovolemia.

Answer question 3:

(a). Incorrect

Phlebotomy is less efficient at removing iron in these patients.

(b). Incorrect

Persons with hemoglobin concentrations lower than 11 mg/dL or hematocrits lower than 0.33 before treatment are more likely to have symptoms of anemia.

(c). Correct

Persons with hemoglobin concentrations lower than 11 mg/dL or hematocrits lower than 0.33 before treatment are more likely to have symptoms of hypovolemia (e.g., hypotension, tachycardia, increased respiratory rate, dizziness, weakness, changes in mental status).

Question 4: **In counseling hemochromatosis patients about diet, which of the following products would you suggest they avoid?**

a. Calcium-rich foods.
b. Iron supplements or multivitamins with iron.
c. Oranges.

Answer question 4:

(a) Incorrect

It is acceptable for hemochromatosis patients to consume calcium-rich foods.

(b). Correct

It is important for hemochromatosis patients to avoid iron supplements or multivitamins with iron.

(c) Incorrect

It is acceptable for hemochromatosis patients to consume natural foods containing vitamin C.

FAMILY-BASED DETECTION MODULE

The family history may be used as a public health tool to identify individuals at risk for disease and thereby facilitate early diagnosis and treatment of those potentially affected.

> "We see so many people in whom the diagnosis of hemochromatosis is made too late – after irreversible damage has already occurred. It's vital that people with hemochromatosis urge family members to get tested immediately. Then, if the condition is detected, treatment can be instituted to prevent organ dysfunction."
>
> Pradyumma D. Phatak, MD, FACP
> Chief, Hematology/Medical Oncology
> Rochester General Hospital.

In the absence of genetic testing, family history can be used as a tool to determine risk for common chronic diseases and thereby identify individuals with increased disease susceptibility.

Content in this module includes:

- Family history as a tool to identify family members at risk.
- Downloadable information for patients and their families.
- Usefulness and limitations of genetic testing.
- Basic genetic counseling.

Patients and their families

A hemochromatosis diagnosis identifies a patient who needs treatment and a family potentially at risk.

Encouraging hemochromatosis patients to urge family members (blood relatives) to have biochemical tests for iron overload, (fasting transferrin saturation and serum ferritin) is an important disease prevention opportunity.

A patient who has hereditary hemochromatosis is often highly motivated to speak to family members about this preventable disease.

Family-based detection is an efficient way to identify those who have an increased risk of developing hemochromatosis, but it requires careful attention to patient confidentiality and preferences.

- Health care providers can facilitate family detection by counseling patients about the value of informing family members.
- A common approach is to give patients printed information about hemochromatosis and a letter for family members that encourages them to be tested for iron overload by their regular health care providers.

Downloadable patient information

Download and print information hemochromatosis patients can share with family members "Talking with Your Family Members about Hemochromatosis". This can be printed on your office letterhead.

Download and print a letter that patients can give family members. This letter can be printed on your office letterhead.

Download and print the CDC brochure "Iron Overload and Hemochromatosis: Information for Patients and their Families". This is a separate pdf document which can be obtained on the World Wide Web.

Talking With Your Family Members About Hemochromatosis

You have been diagnosed with hemochromatosis, a disease that causes your body to absorb too much iron. This condition is usually passed on through genes and may run in families.

Immediate family members who are related to you by birth (blood relatives) need to talk with their doctor about getting a simple blood test to determine if they have too much iron in their body.

Attached is a letter that you can give to your immediate family members (blood relatives) to tell them about hemochromatosis and the blood test they should get.

Family members who are NOT blood related (husband or wife, adopted children, sister-in-law and so forth) do NOT need to see this letter. Only people who are related by blood share the same genes and need to get tested.

Please give a copy of the letter to each of these blood relatives:

- All of your sisters
- All of your brothers
- Your mother
- Your father
- All of your adult children (if you have younger children, be sure to tell your doctor)
- Both of your grandmothers – on mother's AND father's side of the family
- Both of your grandfathers – on mother's AND father's side of the family

If you have questions about this letter, please call our office at _____.

You can learn more about Hemochromatosis on the Internet at the website provided by the Centers for Disease Control and Prevention:

http://www.cdc.gov/nccdphp/dnpa/hemochromatosis/index.htm

Free access to the Internet is available at your local public library.

Department of Health and Human Services
Centers for Disease Control and Prevention

Dear Family Member,

One of our family members is under medical care for hemochromatosis (pronounced he-mo-kro-ma-TOE-sis), a genetic condition that causes the body to absorb too much iron. Because you are a family member related by birth (blood relation), you may have inherited the genes that can cause this disease.

During the early stages of hemochromatosis, most people do not feel sick and cannot tell they have the disease. Without treatment, however, iron can build up in the heart, joints, or pancreas and cause permanent damage. The good news is that complications from hemochromatosis can be prevented if it is found and treated early.

To find out if you have this condition, have your iron status evaluated by your family doctor within the next few months. Two simple blood tests can determine if you have too much iron in your blood: transferrin saturation and serum ferritin. If test results show that you have too much iron, you will need to begin phlebotomy [pronounced flee-BOT-o-me] treatment. This is a safe, simple, and very effective treatment. On a regular basis, patients have blood taken from a vein in the arm, just like donating blood. With proper treatment, people with hemochromatosis can lead long, healthy lives.

Please do not ignore this letter. The special blood tests you need are very simple. Remember, many people who have hemochromatosis feel fine. Finding the disease EARLY is important. Be sure to ask your doctor for these blood tests and talk with your doctor about the results.

Sincerely,

You can learn more about hemochromatosis on the Internet at the website provided by the Centers for Disease Control and Prevention:

http://www.cdc.gov/nccdphp/dnpa/hemochromatosis/index.htm

(Free access to the Internet is available at your local public library.)

Genetic testing

Genetic testing in families with *HFE*-associated hemochromatosis can be particularly useful for determining:

- Who is NOT at increased risk: A family member (blood relative) who has no *HFE* mutations has the same risk of developing hemochromatosis as the general population.
- Whether iron overloading is genetic: In a hemochromatosis patient, finding two *HFE* mutations confirms that his or her iron overloading is genetic and is therefore hereditary hemochromatosis**.**

Genetic testing cannot predict who will develop hemochromatosis.

- Biochemical testing for iron overload (fasting transferrin saturation and serum ferritin) is therefore more clinically relevant than genetic testing for determining which family members have elevated iron measures and need treatment.
- It is important to consider that iron overloading occurs over time. If a family member's serum iron measures are normal now, he or she should have repeat testing every 2-5 years.

Estimates for the risk of inheriting two C282Y mutations for family members related to a patient with two C282Y mutations (*HFE* genotype that confers susceptibility to increased iron absorption) are provided in the table:

Relationship to hemochromatosis patient with two C282Y mutations	**Chance of family member having two C282Y mutations**
None (general population)	1 in 400 (~0.26%)
Brother or sister	1 in 4 (~25.0%)
Parent	1 in 20 (~5.0%)
Child	1 in 20 (~5.0%)
Niece or nephew	1 in 80-160 (~1%)

(Adams PC, 2001)

For example, siblings of an affected person have a 25% chance of having two C282Y mutations. However, not all people with *HFE* gene mutations will develop hemochromatosis (Beutler E, 2002; Bulaj ZJ, 2000; Olynyk JK, 1999).

Counseling patients with genetic test results

While genotyping is an option, insurance discrimination and employment issues should be discussed with the patient before gene tests are performed. Some insurers may misinterpret a demonstration of C282Y/C282Y homozygosity as definite disease, even if iron overloading is not present. Penetrance of H63D mutations for iron loading is quite low.

As a result, genotyping provides less clinically relevant information than do direct iron studies.

Counseling patients about genetic testing and test results is complex and beyond the scope of this website, but basic counseling guidelines are provided in the following table.

Basic counseling

This table provides basic counseling points to consider for patients with different combinations of genotypes and iron study results:

Genotype	Iron study	Counseling points to consider
C282Y/C282Y	Indicate iron overload	A patient who has symptoms has hereditary hemochromatosis – begin treatment. Screen family members – transferrin saturation test.
C282Y/C282Y	Normal	Patient has increased risk of developing hemochromatosis. Monitor iron values every 2-5 years. Patient may have decreased likelihood of needing iron supplements. Screen family members – transferrin saturation test.
C282Y/normal	Normal	Patient is carrier, like 5% of U.S. population. Family does not require testing. Patient is not likely to develop iron overload and may be protected against iron deficiency.
C282Y/H63D	Indicate iron overload	A patient who has symptoms has hereditary hemochromatosis – begin treatment. Screen family members – transferrin saturation test.
C282Y/H63D	Normal	Patient may be at slightly increased risk (<1%)of developing hemochromatosis Monitor iron status every 2-5 years. Screen family members – transferrin saturation test
H63D/H63D	Normal	Patient may have slightly (<1%) increased risk of developing

		hemochromatosis. Monitor iron status every 2-5 years.
H63D/normal	Normal	Patient is carrier, like 13.5% of U.S. population. Family does not require screening. Patient may be protected against iron deficiency.

Summary of family-based detection module

Patients and their families

- A hemochromatosis diagnosis identifies a patient who needs treatment and a family potentially at risk.
- Encouraging hemochromatosis patients to urge family members (blood relatives) to have biochemical tests for iron overload, (fasting transferring saturation and serum ferritin), is an important disease prevention opportunity.
- Download and print on your letterhead information for patients and their families.
    - "Talking with Your Family Members about Hemochromatosis".
    - A letter about family based detection that patients can give family members.
    - CDC brochure titled "Iron Overload and Hemochromatosis: Information for Patients and their Families".

Genetic testing

- Genetic testing in families with *HFE*-associated hemochromatosis can be particularly useful for determining:
    - Who is NOT at increased risk: A family member who has no *HFE* mutations has the same risk of developing hemochromatosis as the general population.
    - If iron overloading is genetic: In a person with hemochromatosis, finding two *HFE* mutations confirms that iron overloading is genetic.

Test your knowledge

This is an optional self-quiz and is not required for continuing education credit. Select the best answers below. If you need help, feel free to review.

(Check the best answer)

Question 1: In a family with known *HFE*-associated hemochromatosis, how often should a family member (blood relative) who has normal biochemical test results for iron overload (fasting transferrin saturation and serum ferritin) have repeated testing?

a. Every 10 years.

b. Every 2-5 years.
c. Annually.

Answer question 1:

(a) Incorrect

Although it is important to consider that iron overloading occurs over time, it is more appropriate to repeat biochemical testing every 2-5 years.

(b). Correct

It is important to consider that iron overloading occurs over time. In a family with known *HFE*-associated hemochromatosis, it appropriate to repeat biochemical testing every 2-5 years unless there is an indication to do so more often.

(c). Incorrect

Unless there is an indication to do so more often, it is appropriate to repeat biochemical testing every 2-5 years in a family with known *HFE*-associated hemochromatosis.

Question 2: In a family with *HFE*-associated hemochromatosis, a blood relative who has no *HFE* mutations has what risk of developing hemochromatosis?

a. The same risk as the general population.
b. Twice as likely to develop hemochromatosis as the general population.
c. Less likely than the general population to develop hemochromatosis.

Answer question 2:

(a). Correct

In a family with *HFE*-associated hemochromatosis, a blood relative who has no *HFE* mutations has the same risk of developing hemochromatosis as the general population.

(b) Incorrect

In a family with *HFE*-associated hemochromatosis, a blood relative who has no *HFE* mutations has the same risk of developing hemochromatosis as the general population.

(c) Incorrect

In a family with *HFE*-associated hemochromatosis, a blood relative who has no *HFE* mutations has the same risk of developing hemochromatosis as the general population.

(Click on all that apply)

Question 3: A limitation of genetic testing is that it CANNOT:

☐ Predict who will develop hereditary hemochromatosis.
☐ Predict who will develop iron overload.

☐ Predict who will develop fatigue and joint pain.

Answer question 3:

A limitation of genetic testing is that it cannot predict

- Who will develop hereditary hemochromatosis.
- Who will develop iron overload.
- Who will develop signs and symptoms of hemochromatosis, such as fatigue and joint pain.

Biochemical testing for iron status (fasting transferrin saturation and serum ferritin) is therefore a more clinically relevant method for determining which family members have elevated iron status and need treatment.

Question 4: In counseling a hemochromatosis patient about family-based detection, which of the following should be included in your discussion?

☐ Encourage the patient to discuss his or her diagnosis with blood relatives, particularly parents, siblings, and grandparents and urge them to visit their doctors to discuss biochemical testing.

☐ Two simple blood tests can be used to determine if a person has iron overload and if he or she requires phlebotomy treatments.

☐ Many people feel fine although they are accumulating iron in body tissues. Therefore, finding the disease early through blood tests is important.

Answer question 4:

All of these should be included in your discussion with the patient.

Urging family members (blood relatives) to undergo biochemical testing is an important disease prevention opportunity.

Many people feel fine although they are accumulating iron in body tissues. Therefore, finding the disease early through blood tests is important.

Biochemical testing is relatively simple and may promote early identification and treatment.

COURSE SUMMARY

Hemochromatosis for Health Care Professionals

Overview of the disease

- The disease, hemochromatosis, a disorder of iron metabolism, occurs as a result of excess iron accumulation in tissues and organs.
- Early detection of iron overload and hemochromatosis treatment can delay or prevent irreversible complications and prolong life.
- The diagnosis of hemochromatosis is often missed, especially when the disease is in its early stages.
- Early non-specific symptoms of hemochromatosis (i.e., fatigue, arthralgias, weakness, weight loss, abdominal pain) resemble various other disease processes.
- Health care professionals therefore need to maintain a high index of suspicion for patients who have early non-specific hemochromatosis symptoms.
- Phlebotomy, the treatment of choice, is relatively easy, safe, and inexpensive.

Pathophysiology module

Iron overload

- Iron overload is the accumulation of excess iron in body tissues.
- Once iron is absorbed, there is no physiologic mechanism for excretion of excess iron from the body other than blood loss i.e., pregnancy, menstruation or other bleeding.
- Iron is bound and transported in the body via transferrin and stored in ferritin molecules.
- The liver and heart are especially vulnerable.

Hemochromatosis

- Hemochromatosis is a disease that occurs as a result of significant iron overload. It can have genetic (majority of cases) or non-genetic causes.
- Men tend to become symptomatic in middle age (40s) and women who stop menstruating develop symptoms about 15 years later.

HFE gene mutations

- *HFE* gene mutations can lead to iron overloading.

Hereditary hemochromatosis

- Hereditary hemochromatosis is the genetic disease that results from significant iron overload.
- The majority of hereditary hemochromatosis (also known as Type 1 Hemochromatosis) is associated with homozygous mutations in the *HFE* gene.
- People with *HFE* mutations absorb a few extra milligrams of iron per day. Over decades, this leads to iron overloading that can lead to disease.

Epidemiology module

Prevalence

- Reported U.S. population prevalence estimates of iron overloading (based on random non-fasting elevated TS values) range from 1% to 6%.
- A lower percentage of people who initially have a random elevated TS also have persistently elevated TS: estimates range from 35% to 50%.
- An even lower percentage of people with persistently elevated TS measures also have elevated serum ferritin values.
- Thus, the proportion of people who will develop clinical signs and symptoms of hemochromatosis is even lower than the proportion of people with elevated SF values.

HFE gene mutations

- Two *HFE* gene mutations, C282Y and H63D, account for the majority of hereditary hemochromatosis cases; C282Y is most common.
- *HFE* hereditary hemochromatosis is inherited in an autosomal recessive pattern.

HFE genotype frequencies

- The population prevalence of *HFE* mutations depends on race and ethnicity but is most prevalent among persons of European origin and descent.

Penetrance

- Of people with *HFE* gene mutations, only a subset will develop an elevated TS. Of those with an elevated TS, only a subset will develop an elevated SF. Of those with an elevated SF, only a subset will develop hemochromatosis symptoms. Of those with symptoms, only a subset will develop clinical signs consistent with hemochromatosis
- Most clinicians reserve the hemochromatosis diagnosis for patients whose signs and symptoms are clearly referable to documented iron overload as reflected by serum iron testing measurements.
- Iron status testing is more clinically relevant than genetic testing for identifying those who have hemochromatosis.

Population screening

- At this time, CDC does not recommend population screening for *HFE* gene mutations because of the uncertainty about what proportion of people with *HFE* gene mutations will develop hemochromatosis.

Clinical features module

Clinical expression

- The iron accumulation rate and the frequency and severity of clinical symptoms vary widely and may be dependent on factors such as age, gender, and diet.

Early stages

- The most commonly associated early hemochromatosis symptoms are non-specific and may include
    - Fatigue.
    - Weakness.
    - Weight loss.
    - Abdominal pain.
    - Arthralgia.

- As iron accumulation progresses, patients may also experience
    - Arthritis.
    - Symptoms of gonadal failure.
    - For example, amenorrhea, early menopause, loss of libido, impotence.
    - Shortness of breath/dyspnea.

- Maintain a high index of suspicion of hemochromatosis for patients with early signs or symptoms of this disease.

Advanced stages

- Iron accumulates in the parenchymal cells of several organs; the liver is a major site followed by the heart and pancreas.
- The liver is usually the first organ to be affected, but signs of organ damage occur in the later stages of the disease.

Primary disorders associated with advanced hemochromatosis

- Most advanced hemochromatosis complications are also common primary disorders.
- A hemochromatosis diagnosis can be missed even in advanced stages unless looked for specifically.

Diagnostic testing module

Biochemical testing

- Biochemical testing for iron status is recommended for patients with
    - Symptoms or signs suggestive of hemochromatosis:
    - Porphyria, hepatitis or other liver diseases.
    - Abnormal blood tests consistent with hemochromatosis:
- Evaluation for other causes of these medical problems should also be performed.
- Testing is also recommended for family members of diagnosed patients.
- Recommended laboratory iron tests for the workup of a patient you suspect may have hemochromatosis are
    - Fasting transferrin saturation test (TS)
    - Serum ferritin test (SF)

Testing protocol

- Transferrin saturation (TS).

    - Fasting values >45% should be followed by a serum ferritin test and additional workup.
- Serum ferritin (SF)
    - Values >200 ng/mL for premenopausal females OR >300 ng/mL for postmenopausal females and males indicate iron overload; phlebotomy treatment is warranted in the absence of other causes.
    - SF values can be elevated with liver disease, inflammation, and neoplasm.
- Confirmation of iron overload is typically required
    - Most health care providers consider quantitative phlebotomy the confirmatory test of choice.
    - Genotyping for *HFE* mutations can provide additional confirmatory evidence that a patient has hereditary hemochromatosis.
    - Many authorities once considered liver biopsy an essential diagnostic test, but it is now used more often as a prognostic, rather than a diagnostic, test.

Treatment and management module

Phlebotomy treatment

- Therapeutic phlebotomy is the preferred treatment for reducing iron stores in hemochromatosis patients.
- For a patient who has no evident tissue or organ damage, proper disease management may result in normal long-term outcome and life expectancy.

Phlebotomy regimen

- Clinicians must design phlebotomy treatment regimens that are individualized to each patient and account for age, gender, weight, health, and likelihood of compliance.

Monitoring treatment

- Serum ferrinin levels should be measured after each additional one or two phlebotomy treatments once the value is ≤ 100 ng/mL.
- Careful monitoring of each patient throughout treatment is imperative. If treatment is too aggressive, anemia may result.

Lifetime maintenance

- Continued lifetime monitoring is key to appropriate management.
- Phlebotomy should be performed throughout a patient's life to keep the serum ferritin level between 25 and 50 ng/mL.

Compliance

- Download and print on your office letterhead "Phlebotomy Information for Patients with Hemochromatosis".
- Hemochromatosis cannot be treated by diet alone.
- The following dietary modifications for patients are suggested:
    - Avoid iron supplements.

    - Read the label of multivitamins to make sure they do not contain iron.
    - Limit vitamin C supplementation to 500 mg/day.
    - Avoid eating raw shellfish.
    - Avoid more than moderate alcohol consumption. Patients with liver damage should avoid alcohol.
    - Download and print on your office letterhead "Diet Information for Patients with Hemochromatosis."
- Download and print on your office letterhead "Diet Information for Patients with Hemochromatosis".

Family based detection module

Patients and their families

- A hemochromatosis diagnosis identifies a patient who needs treatment and a family potentially at risk.
- Encouraging hemochromatosis patients to urge family members to have biochemical tests for iron overload, (fasting transferring saturation and serum ferritin), is an important disease prevention opportunity.
- Download and print on your letterhead information for patients and their families.
    - "Talking with Your Family Members about Hemochromatosis".
    - A letter about family based detection that patients can give family members.
    - CDC brochure titled "Iron Overload and Hemochromatosis: Information for Patients and their Families".

Genetic testing

- Genetic testing in families with *HFE*-associated hemochromatosis can be particularly useful for determining:
    - Who is NOT at increased risk: A family member who has no *HFE* mutations has the same risk of developing hemochromatosis as the general population.
    - If iron overloading is genetic: In a person with hemochromatosis, finding two *HFE* mutations confirms that iron overloading is genetic.

CASE STUDIES MODULE

Interactive case studies allow you to practice your skills in diagnosing, treating and managing hemochromatosis patients.

After completing the case studies, you will be able to:

- Identify early symptoms of hemochromatosis.
- Order blood tests necessary to assess iron status.
- Identify appropriate treatment options for hemochromatosis patients.
- Order tests used to monitor iron levels before, during, and after phlebotomy treatments.
- Describe dietary modifications for hemochromatosis patients.
- Make recommendations for family-based detection.

You will review the records of five patients:

- Michael, a middle-aged man with non-specific complaints and a suggestive family history.
- Marie, a woman with no significant family history.
- Claire, a healthy young woman with a positive family history.
- Patrick, a middle-aged African American man.
- Jon, a healthy young man with no family history.

These case studies were written for educational purposes and are not actual patients.

Michael

Case Study 1: A middle-aged man with non-specific complaints and a suggestive family history.

Michael is a 46-year-old white male of European descent with complaints of joint pain in his knees and hands. He also states he is concerned because two siblings died in the past year.

Past medical history:

- Numerous office visits over 3-4 years for complaints of fatigue, weakness, and pain.
- Denies routine blood donation.

Family history:

- Father died at age 55 from myocardial infarction.
- Mother alive and apparently healthy.
- Brother died at age 53 of esophageal varices. Autopsy records indicate the liver showed evidence of iron overload.
- Sister died at age 49 of liver cancer. Autopsy records for sister are not available.
- Brother age 43 alive and apparently healthy.
- Sister age 40 alive and apparently healthy.

Social history:

- Drinks "a couple of beers a week," denies tobacco use, denies recreational drug use.
- Denies multivitamin use.

Physical exam:

- Mild hepatomegaly.
- Modest enlargement of the second and third metacarpal-phalangeal joints.
- Knees have no effusions.
- Height: 5'11" Weight: 195 lbs.
- Vital signs within normal limits.

After reviewing Michael's medical record, please respond to the questions below with your best possible answers. Response formats vary within the case study. Some questions will be open-ended, requiring you to compare your response to the expert opinion. Other questions will be multiple choice or drop-down choices.

Question 1
In the space below, type the factors that may affect the clinical expression of hemochromatosis. Also type signs and symptoms that would heighten your suspicion that Michael may have hemochromatosis:

Michael had a random TS test 2 years ago.
The result was 65%. Michael vaguely remembers this and states, "It seemed unimportant at the time."

Serum iron and total iron-binding capacity were collected from a fasting draw, these allow for calculation of transferrin saturation. Serum ferritin was also collected.

Michael's lab results:

Serum ferritin	1000 ng/mL
Transferrin saturation (fasting)	97%
Hemoglobin	13.5
Hematocrit	40%
ALT	2 × normal
AST	2 × normal

Question 2
Type the treatment plan for Michael in the space below:

Question 3
Complete the order form below to initiate quantitative phlebotomy:

Phlebotomy mL of whole blood (drop-down menu with these options to click: 250 mL, 500 mL, 750 mL) (drop-down menu indicating frequency of treatments: once per week, once per month, once every 3 months) with careful monitoring of the appropriate blood tests over the course of phlebotomy treatments.

Question 4
Type the points you would cover in your discussion with Michael in the space below:

Question 5
As you discuss the plan of care with Michael, he asks if he should follow any dietary restrictions or modifications. Which of the following dietary modifications would you suggest? (click all that apply).

☐ Avoid iron supplements or multivitamins with iron.
☐ Eliminate alcohol consumption.
☐ Avoid eating raw shellfish.
☐ Limit vitamin C supplements to 500 mg/day. Eating natural foods with vitamin C is fine.

Answers:
Question 1
Factors that may affect the clinical expression of hemochromatosis include

- Age.
- Ethnic origin.
- Gender.
- No history of iron supplement use.
- History of alcohol consumption.
- No history of routine blood donation.
- Suggestive family history.

Clinical signs and symptoms suggestive of hemochromatosis

- Joint pain.
- Hepatomegaly.
- Enlargement of metacarpal-phalangeal joints.
- History of unexplained fatigue, weakness, and pain.

Question 2
The treatment plan

- Quantitative phlebotomy.
    - Monitor serum ferritin every 4-8 weeks over the course of phlebotomy treatments.
    - Continue to monitor patient's health status, hemoglobin, and hematocrit, over the course of the phlebotomy treatments.
- Exclude other causes for elevated serum ferritin, such as inflammation and neoplasm.
- Referral to a hepatologist for further evaluation of liver function.

Question 3
Phlebotomy treatments

- Phlebotomy 500 mL of whole blood every week with careful monitoring of appropriate blood tests over the course of phlebotomy treatments.
- Monitor serum ferritin every 4-8 weeks over the course of phlebotomy treatments.
- Continue to monitor patient's health status, hemoglobin, and hematocrit over the course of phlebotomy treatments.

Question 4
Your discussion with the patient includes

- Pre- and post-phlebotomy instructions.
- Family-based detection, urging the patient to encourage his mother, brother, and sister to undergo biochemical testing.
- Genetic testing options.
- Advice to eliminate drinking alcoholic beverages due to elevated liver function test results.
- Dietary modifications as an adjunct to phlebotomy treatment.

Question 5
Dietary modifications you suggest include

- Avoid iron supplements or multivitamins with iron.
- Eliminate alcohol consumption.
- Avoid eating raw shellfish.
- Limit vitamin C supplements to 500 mg/day. Eating natural foods with vitamin C is fine.

Summary of case study

- Michael visited multiple doctors before receiving the correct diagnosis.
- Family history is highly suggestive; his brother's autopsy records indicate the presence of iron in the liver.
- The serum ferritin of 1000 ng/mL and elevated ALT and AST levels require follow up with a hepatologist. Results of a liver biopsy may help confirm iron overload, exclude other co-existent liver pathology and determine the prognosis. If cirrhosis is present, this may warrant ongoing follow-up for early detection of hepatoma and signs of liver dysfunction.
- Instructions to Michael about his diet, as an adjunct to phlebotomy treatment:
    - Avoid using iron supplements or multivitamins containing iron.
    - Avoid using alcoholic beverages.
    - Avoid eating raw shellfish.
    - Limit vitamin C supplements to 500 mg/day
- The patient should be encouraged to discuss his diagnosis with family members and urge them to have their iron status evaluated with biochemical testing.

Marie

Case Study 2: A woman with no significant family history who may be susceptible.

Marie is a 69-year-old French-American woman with complaints of fatigue and feeling "weak and tired." She states she has "lost interest in doing the things I normally enjoy." She also complains of pain in her knees.

Past medical history:

- Patient has been healthy and active.
- Denies blood donation.

Family history:

- Mother died at age 75 of cancer.
- Father died at age 78 of a stroke.
- Brother age 65, alive and apparently healthy.

Social history:

- Three adult children apparently alive and healthy.
- Denies tobacco use, denies alcohol consumption, denies recreational drug use.

Physical exam:

- Mild effusion in left knee.
- Height: 5'2" Weight: 105 lbs.
- Vital signs within normal limits.

After reviewing Marie's medical record, please respond to the questions below with your best possible answers. Response formats vary within the case study. Some questions will be open-ended, requiring you to compare your response to the expert opinion. Other questions will be multiple choice or drop-down choices.

Question 1

In the space below, type the factors that may affect the clinical expression of hemochromatosis. Also, type the signs and symptoms that would heighten your suspicion that Marie may have hemochromatosis:

Based on the suggestive history, fasting serum iron and total iron-binding capacity were ordered, these allow for calculation of transferrin saturation. Serum ferritin was also ordered. In the clinical setting, additional lab tests may be indicated.

Marie's lab results:

Serum ferritin	700 ng/mL
Transferrin saturation (fasting)	97%
Hemoglobin	14
Hematocrit	42%
ALT	Within normal limits
AST	Within normal limits

Additional workup is negative for other possible causes of elevated iron levels. As you counsel Marie, you discuss family-based detection and urge her to encourage

siblings and children to undergo biochemical testing. You also discuss dietary modifications as an adjunct to phlebotomy treatment.

Question 2
Complete the form below to initiate Marie's phlebotomy treatment:

Phlebotomy mL (drop-down menu with these options to click: 250 mL, 500 mL, 750 mL) of whole blood (drop-down menu indicating frequency of treatments: once per week, once per month, once every 3 months) with careful monitoring of appropriate blood tests over the course of phlebotomy treatments.

Monitor serum ferritin every 4-8 weeks over the course of phlebotomy treatments. Continue to monitor patient's health status, hemoglobin, and hematocrit over the course of phlebotomy treatments.

Follow-up visit:
Marie returns to the office for a follow-up visit. She has undergone weekly phlebotomies of 250 mL for 10 months. She now complains of feeling "dizzy and lightheaded." Serum ferritin is drawn and is 8 ng/mL.

Question 3
Type the treatment plan for Marie in the space below:

Answers
Question 1
Factors that may affect the clinical expression of hemochromatosis include

- Age.
- Ethnic origin.
- Gender.
- History of childbearing.
- No history of iron supplement use.
- No history of alcohol use.
- No history of routine blood donation.

Clinical signs and symptoms suggestive of hemochromatosis

- Fatigue.
- Painful joints.
- Effusion in left knee.

Question 2
Phlebotomy treatments

- Phlebotomize 250 mL of whole blood every week with careful monitoring of appropriate blood tests over the course of phlebotomy treatments. Elderly adults of small build may require adjustment in the amount of phlebotomy.
- Monitor serum ferritin every 4-8 weeks over the course of phlebotomy treatments.

Continue to monitor patient's health status, hemoglobin, and hematocrit over the course of phlebotomy treatments.

Question 3

The treatment plan

- Discontinue phlebotomy treatments until serum ferritin returns to ~25-50 ng/mL.
- Resume phlebotomy treatments of 250 mL of whole blood as needed every 3-6 months to maintain serum ferritin at ~25-50 ng/mL.
- Continue to monitor patient's health status, hemoglobin, and hematocrit over the course of phlebotomy treatments.

Summary of case study

- The patient's genotype is unknown.
- Her family history is not suggestive of hemochromatosis.
- She exhibits evidence of iron overload through biochemical measurements.
- Regardless of genotype, her hemochromatosis should be treated with phlebotomy.
- This case study demonstrates the importance of monitoring serum ferritin levels and other appropriate blood tests over the course of phlebotomy treatment.
    - Anemia may result if treatment is too aggressive. Elderly adults of small build may require adjustment in the amount of phlebotomy.
- The patient should be encouraged to urge family members to have their iron status evaluated with biochemical testing.

Claire

Case Study 3: A young healthy woman with a positive family history.

Claire is a 36-year-old Irish-American female with no health-related complaints. Her brother was recently diagnosed with hemochromatosis. After talking with him and researching hemochromatosis on the Internet, she decided to make an appointment for a routine physical exam and discuss her health concerns with her primary care provider.

Past medical history:

- No significant past medical history.
- Two normal pregnancies; two healthy preschool-aged children.
- Uses oral contraceptives.
- Denies routine blood donation.

Family history:

- Father alive and healthy at age 67.
- Mother alive with arthritis at age 63.
- Brother age 42 has "heart problems" and was recently diagnosed with hemochromatosis. Genetic testing results: homozygote (C282Y/C282Y).
- Sister age 38 alive and apparently healthy. DNA analysis: heterozygote (C282Y/normal).
- Sister age 34 alive and apparently healthy.

Social history:

- Denies tobacco use, denies alcohol consumption, denies recreational drug use.
- States she eats a healthy diet, including 6-8 servings of fruits and vegetables a day; avoids eating red meat.
- Denies multivitamin use.

Physical exam:
- Normal.
- Height: 5'5" Weight: 135 lbs.
- Vital signs within normal limits.

After reviewing Claire's medical record, please respond to the questions below with your best possible answers. Response formats for responding vary within the case study. Some questions will be open-ended, requiring you to compare your response to the expert opinion. Other questions will be multiple choice or drop-down choices.

As you counsel Claire, she states that she is not willing to undergo genetic testing due to a recent job change and a concern that she may be denied medical insurance.

Question 1
In the space below, type the option you would discuss with Claire, and explain your rationale for that option:

Question 2
Use the order form below to check the most appropriate blood test(s) to order to evaluate Claire's iron status. In the clinical setting, additional blood tests might be ordered, including hemoglobin and hematocrit.

☐ Serum ferritin.
☐ Serum iron (fasting blood draw).
☐ Total iron-binding capacity (fasting blood draw).

Question 3
Remember to advise Claire to discontinue use of which of these products 24 hours prior to her fasting blood draw:

☐ Iron supplements.
☐ Iron containing placebos found in some oral contraceptive packages
☐ Vitamin C supplements.

Claire's lab results:

Serum ferritin	35 ng/mL
Transferrin saturation (fasting blood draw)	20%
Hemoglobin	13
Hematocrit	38%

Question 4
Type the treatment plan for Claire in the space below:

Answers
Question 1
You can reassure Claire that it is possible to monitor her iron status through biochemical testing.
Your rationale to suggest this treatment option includes

- Biochemical measures are more clinically relevant and can determine whether Claire is loading iron.
- Biochemical evaluation avoids the possibility of adverse genetic discrimination (e.g., ethical, legal, and social issues).

Question 2
In light of her family history of siblings with *HFE* gene mutations, it would be appropriate to order serum iron and total iron-binding capacity collected from a fasting blood draw. This allows calculation of transferrin saturation from a fasting blood draw. Serum ferritin can also be ordered at this time.

Question 3
Each of these products should be discontinued for 24 hours prior to her fasting blood draw.

Question 4
Treatment plan:

- Reassure Claire that her iron status is within normal limits.
- Re-evaluate iron status in 2-5 years unless unexplained signs and symptoms warrant evaluation.
- Encourage Claire to discuss family-based detection with her parents, sister, and grandparents and urge them to undergo biochemical testing.

Summary of case study

- A patient with genetic predisposition for hereditary hemochromatosis needs biochemical testing to check for iron overloading.
- The known family history helps with in the evaluation.
- Biochemical measures can confirm the absence of iron overload.
- Patient should be re-evaluated for iron overloading in 2-5 years.

Patrick

Case Study 4: An African American man may be susceptible to hemochromatosis.

Patrick is a 50-year old-overweight African American male with complaints of abdominal pain.

Past medical history:

- Recently diagnosed with diabetes, which is well controlled by diet and oral agents.

- Denies routine blood donation.

Family history:
- Mother age 75 with adult-onset diabetes and arthritis.

Social history:
- Drinks a glass of wine occasionally with dinner, denies use of tobacco, denies use of recreational drugs.
- Eats red meat and "fried foods." Denies eating raw shellfish.

Physical exam:
- Possible palpable liver.
- Height: 5'10" Weight: 205 lbs.
- Vital signs: Within normal limits.

After reviewing Patrick's medical record, please respond to the questions below with your best possible answers. Response formats vary within the case study. Some questions will be open-ended, requiring you to compare your response to the expert opinion. Other questions will be multiple choice or drop-down choices.

Question 1
Although hemochromatosis typically affects people of European descent, what factors may contribute to the clinical expression of hemochromatosis? Include signs or symptoms that would cause you to consider the possibility of iron overload in this patient. Type your answers in the space below.

A fasting specimen was collected to measure serum iron and total iron-binding capacity, which allows for the calculation of transferrin saturation. Serum ferritin was also obtained.

Patrick's lab results:

Serum ferritin	290 ng/mL
Transferrin saturation (fasting blood draw)	43%
Hemoglobin	14
Hematocrit	40%
ALT	2 × normal
AST	2 × normal

Question 2
Type the treatment plan for Patrick in the space below:

Question 3

Type the points you would cover in your discussion with Patrick in the space below:

Answers:

Question 1

Factors that may affect the clinical expression of hemochromatosis include

- Age of onset.
- Ethnic origin.*
- Gender.
- No history of iron supplement use.
- History of alcohol consumption.
- No history of routine blood donation.

* Although it is rare to find *HFE* mutations in African Americans with iron overload (McNamara L, 1998), these mutations have been found in a few individuals (Barton JC and Acton RT, 2000, 2001). It has been suggested that their appearance is due to admixture. Current research suggests that genes other than *HFE* are responsible for the majority of iron overload in African Americans.

Clinical signs and symptoms suggestive of hemochromatosis include

- Diabetes
- Complaints of abdominal pain
- Hepatomegaly

Question 2

The treatment plan:

- Refer to a hepatologist to evaluate elevated AST and ALT.
- Monitor liver function over time.
- Re-evaluate iron status in 2-5 years.
- Follow diabetes as needed to maintain good blood-glucose control.
- Monitor weight and develop a weight loss plan.

Question 3

Your discussion with the patient includes

- Reassurance that his iron status is within normal limits.
- An explanation that family-based detection is not needed; he is at low risk for hemochromatosis.
- Encouraging the patient to lose weight and discussion of the weight loss plan.
- Recommendation to avoid alcohol consumption due to elevated liver function tests.

Summary of case study

- African Americans may be at risk for hemochromatosis. Patrick's symptoms are vague and required evaluation of serum iron measures.
- Although it is rare to find *HFE* mutations in African Americans with iron overload (McNamara L, 1998), these mutations have been found in a few individuals (Barton JC and Acton RT, 2000 and 2001). It has been suggested that their appearance is due to admixture. Current research suggests that

genes other than *HFE* are responsible for the majority of iron overload in African Americans.
- The patient's liver disease does not appear to be related to iron overload.

Jon

Case Study 5: A healthy young man with no family history of hemochromatosis.

Jon is a 36-year-old white male of British descent with no complaints. He is an executive and recently completed an annual physical exam as required by his employer. Blood collected for screening purposes, revealed a random elevated transferrin saturation of 82%.

Past medical history:
- No significant past medical history.
- Denies routine blood donation.

Family history:
- No significant family history.

Social history:
- Active and apparently healthy.
- Single, no children.
- Denies alcohol use, denies recreational drug use, denies tobacco use.
- Takes a multivitamin daily but is not sure if it contains iron; enjoys oysters on the half shell and sushi; denies eating red meat or organ meat; denies drinking coffee, teas, or caffeinated beverages.

Physical exam:
- Normal.
- Height: 5'10" Weight: 185 lbs.
- Vital signs: within normal limits.

Jon's lab results are

Serum ferritin	600 ng/mL
Transferrin saturation (fasting)	80%
Hemoglobin	14.5
Hematocrit	44%
ALT	normal
AST	normal

Progress note:
The treatment plan:
- Quantitative phlebotomy of 500 mL of whole blood per week with careful monitoring of appropriate blood tests.
- Monitor serum ferritin every 4-8 weeks over the course of phlebotomy treatments. Continue to monitor patient's health status, hemoglobin, and hematocrit over the course of the phlebotomy treatments.

Your discussion with the patient includes:
- Pre- and post-phlebotomy care.

- Family-based detection for siblings and parents and the importance of urging them to undergo biochemical testing.
- Options for genetic testing.
- Based on his social history, dietary modifications as an adjunct to phlebotomy treatment. In particular, clarify that he should eliminate iron supplements and multivitamins containing iron, and consumption of raw shellfish.

After reviewing Jon's medical record and most recent progress note, please respond to the questions below with your best possible answers. Response formats vary within the case study. Some questions will be open-ended, requiring you to compare your response to the expert opinion. Other questions will be multiple choice or drop-down choices.

Follow-up office visit:
Jon has undergone phlebotomy treatments extracting 500 mL of whole blood weekly for approximately 5 months. His serum ferritin level is now 48 ng/mL. He has no complaints related to phlebotomy treatment.

Question 1
The most appropriate lab test to order to monitor Jon's iron status and manage his phlebotomy treatments over the course of his life is (drop-down menu with these options to click: serum ferritin, transferrin saturation, serum iron).
The ideal maintenance range for this blood value is (drop-down menu indicating 25-50 ng/mL, 55-75 ng/mL, 75-100 ng/mL).

Question 2
Complete the form below to indicate the plan for Jon's maintenance phlebotomy regimen:

Phlebotomy mL (drop-down menu with these options to click: 250 mL, 500 mL, 750 mL) of whole blood (drop-down menu indicating frequency of treatments: once per week, once per month, once every 3 months).

Answers:

Question 1
Serum ferritin is the most useful measure for monitoring iron status. The ideal maintenance range is ~25-50 ng/mL.

Question 2
Maintenance phlebotomy:
Phlebotomize 500 mL of whole blood approximately every 3 months.

Note: Additional monitoring of patient's health and measuring other lab values (i.e., hemoglobin concentration and hematocrit) are also appropriate.

Summary of case study
- During the course of his routine yearly physical exam, a wide panel of blood tests were ordered for this patient.
- The elevated transferrin saturation led to the early detection of iron overloading and early intervention with phlebotomy in this patient who has no signs, symptoms, or family history.

- Instruct the patient about his diet as an adjunct to phlebotomy treatment: Avoid using iron supplements or multivitamins containing iron, and avoid eating raw fish and shellfish.
- The patient should be encouraged to discuss his diagnosis with family members and urge them to have their iron status evaluated with biochemical testing.

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GLOSSARY

Alanine aminotransferase (ALT)	ALT is found in blood serum and in certain body tissues, especially hepatic tissues. It is released into the bloodstream by injury or disease affecting the liver (see SGPT).
Alleles	Alternate forms or varieties of a gene. Alleles for a trait occupy the same locus or position on homologous chromosomes and thus govern the same trait.
Amenorrhea	Absence or abnormal stoppage of menstruation; also called amenia.
Anemia	Iron deficiency leading to decreased red blood cell levels and insufficient amounts of hemoglobin and myoglobin, resulting in weakness, fatigue, susceptibility to infection, and paleness.
Arrhythmia	Any variation from the normal heart beat rhythm, including sinus premature beat, heart block, atrial fibrillation, atrial flutter, and paroxysmal tachycardia.
Arthralgia	Joint pain.
Arthropathy	Any joint disease.
Aspartate aminotransferase (AST)	A hepatic enzyme released into the blood when certain organs or tissues, particularly the liver and heart, are injured. AST is also known as serum glutamic oxaloacetic transaminase (SGOT).
Autosome	Any chromosome other than a sex chromosome. Humans have 22 pairs of autosomal chromosomes; and the *HFE* gene is on autosomal chromosome 6.
C282Y mutation	A missense mutation that causes the amino acid tyrosine to replace a cysteine at position 282 in the HFE protein, which normally helps regulate iron uptake. This causes the HFE protein to misfold and malfunction, which can lead to increased iron absorption. About 5 of every 1,000 Americans of European dissent are homozygotes for this mutation.
Cardiomyopathy	General diagnostic term designating primary myocardial disease that may lead to chronic heart disease.
Carrier	An individual who has one copy of a mutant allele that causes disease only when two copies are present. Although the associated disease does not affect carriers, two carriers can produce a child who has the disease.
Chelation therapy	The use of a ring-shaped compound, or iron-chelating agent, capable of forming complexes with circulating iron and assisting in its removal from the body (see deferoxamine).
Chromosome	A threadlike package of genes and other DNA in the cell nucleus. Humans have 23 pairs of chromosomes; 44 autosomes, and 2 sex chromosomes. Children get half their chromosomes from the mother and half from the

	father.
Cirrhosis	Cirrhosis is a disease characterized by scarring of the liver, causing fibrosis and nodular regeneration. Destruction of normal liver architecture prevents the liver from properly digesting food, metabolizing drugs, or making proteins. Cirrhosis is a serious condition.
Deferoxamine (desferal Rx)	Iron-chelating agent used therapeutically to treat acute iron intoxication or chronic iron overload in transfusion-dependent patients. May also be used to treat hemochromatosis in patients such as anemics who cannot tolerate phlebotomy. It forms a water-soluble complex with iron that is excreted in urine and feces (see chelation therapy).
Diabetes mellitus type I	The islets of Langerhans are destroyed as a consequence of genetic susceptibility, followed by the onset of autoimmune destruction triggered by an environmental factor such as a viral infection. The number and size of insulin-producing cells in the pancreas are eventually reduced, leading to decreased insulin production and glucose intolerance.
Diabetes mellitus type II	A chronic disease that results when the body's insulin does not effectively move glucose from the blood to the interior of cells. Excess glucose builds up in the blood and is removed by the kidneys, resulting in excessive thirst, frequent urination, hunger, fatigue, weight loss, and increased insulin production.
Diagnostic test	Blood testing used when a specific disease is suspected, to verify the disease's presence and severity (see TS and SF).
Erythropoiesis	The production of erythrocytes, or red blood cells.
Fasting blood draw	For a fasting blood draw, avoid the following items 24 hours prior to blood draw: vitamin C, nutritional supplements, medicinal iron or estrogen preparations, iron containing placebos found is some oral contraceptive packages, and alcohol.
Ferritin	Iron-storage protein. (see serum ferritin).
Free radicals	Highly reactive molecules with unsatisfied electron valence pairs, capable of causing massive tissue damage and enhancing the effects of aging. Elevated iron levels increase the occurrence of free radical formation in the body.
Genetic screening	Testing of a population group to identify a subset of individuals who carry a genetic mutation (H63D, C282Y) and are consequently at higher risk for having or transmitting a specific genetic disorder. Patients should receive counseling before undergoing genetic screening.
Genotype	The genetic identity of an individual that does not contribute to outward characteristics. Genetic makeup.
H63D mutation	A missense mutation that causes the amino acid aspartate to replace a histidine at position 63 in the HFE protein, which can lead to primary iron overload. H63D

	has an allele frequency of approximately 16% in the U.S. general population.
Hematocrit	The percentage of packed red blood cells found in a unit volume of blood. Normal levels are 35%-45% for females and 40%-50% for males.
Heme iron	The iron found in the hemoglobin and myoglobin of foods such as meat, poultry, and fish. It is 2-3 times more absorbable than nonheme iron.
Hemochromatosis	The disease that occurs as a result of significant iron overload. Hemochromatosis can have genetic and non-genetic causes.
Hemoglobin	The protein that gives red blood cells their color; about 75% of the body's iron is bound to hemoglobin and involved in oxygen transport from the lungs to the rest of the body. Regular levels are approximately 16 g/dL for men and 14 g/dL for women.
Hemolytic anemia	Anemia caused by the destruction of red blood cells by a disease process. Occurs in newborns as a result of blood-group incompatibility between mother and baby. It is also caused by abnormal red cell membranes or abnormal hemoglobin, i.e., sickle cell anemia and thallassemia. Complications include all the ill effects of profound anemia as well as possible problems caused by jaundice.
Hemosiderin	An iron-containing pigment formed when the potential to store iron as ferritin is exceeded; a type of storage iron.
Hemosiderosis	Excessive iron accumulation due to transfusion, medication, dietary overload, and other reasons. May produce the same pathologic changes as hereditary hemochromatosis.
Hepatic biopsy	Removal of a small piece of liver tissue for microscopic examination or testing. A liver biopsy can be used to confirm the hemochromatosis diagnosis by assessing the amount of iron per gram in liver tissue.
Hepatic enzymes	Various enzymes (ALT, SGPT, AST, SGOT, and GGT) that leak into the bloodstream as a result of injury to liver cells from infection, iron overload, or bile flow obstruction. Elevated enzymes are suggestive of liver damage.
Hepatic iron concentration	The amount of iron in the liver. Measured by atomic absorption spectrophotometry of hepatic parenchymal cells or histologically with Perl's stain. Normal values are <80 mol/g dry weight; >80 mol/g indicates overload.
Hepatitis	Inflammation of the liver.
Hepatocellular carcinoma	A malignant growth made up of liver epithelial cells that tend to infiltrate the surrounding tissues and give rise to metastases. Liver cancer.
Hepatomegaly	Enlargement of the liver.
Hereditary hemochromatosis	The genetic disease that results from significant iron overload. The majority of hereditary hemochromatosis (also known as Type I Hemochromatosis) is associated with homozygous mutations in the *HFE* gene. There are other heritable forms, associated with other genes.

Heterozygous	Possessing two different forms (alleles) of a particular gene, one inherited from each parent.
***HFE* gene**	The gene-encoding translation of the HFE protein, which plays a roll in iron absorption. Mutations of this gene can predispose to developing primary iron overload. An estimated 10% of the U.S. population carries an *HFE* gene mutation.
***HFE* gene mutations**	The *HFE* gene protein product is a transmembrane glycoprotein that modulates iron uptake. Mutations in this gene compromise its function and can lead to iron overloading.
HFE protein	An HLA-like protein that is expressed on the surface of duodenal crypt enterocytes and participates in iron uptake and transport. Mutations in this gene appear to cause these cells to lose the ability to sense the level of body iron stores.
Homozygous	Possessing two identical forms (alleles) of a particular gene, one inherited from each parent. Individuals who are homozygous for a trait are referred to as homozygotes.
Hyperferremia	High levels of serum iron caused by random iron overload (repeated transfusions, primary hemochromatosis), liver disease, disordered or decreased erythropoiesis, or hemolytic anemia.
Hyperthyroidism	Overactive thyroid.
Hypotension	Abnormally low blood pressure.
Hypothyroidism	Underactive thyroid.
Hypovolemia	Abnormally decreased volume of blood circulating in the body.
Iron overload	The accumulation of excess iron in body tissues. Iron overload usually occurs as a result of a genetic predisposition to absorb iron in excess of normal. Iron overload can also occur as a complication of: • Other hematologic disorders, e.g., inherited and acquired anemias. • Chronic transfusion therapy or repeated injections of iron dextram. • Chronic hepatitis. • Excessive iron ingestion.
Juvenile hemochromatosis	A non-*HFE* hemochromatosis in a person younger than age 30. Also known as Hemochromatosis Type 2A or 2B. (see Heritable and Acquired Disorders Associated with Iron Overload)
Missense mutation	A nucleotide substitution within a gene that changes a codon so that it codes for a different amino acid in the protein. This usually changes the activity of the protein.
Neoplasm	Any new and abnormal tissue growth.
Non-alcoholic steatohepatitis (NASH)	A liver that contains fatty deposits and shows evidence of inflammation but has not been damaged by alcohol.

Nonheme iron	The iron in plant-based and iron-fortified foods.
Penetrance	The proportion of individuals with a specific genotype who manifest the genotype at the phenotype level. In other words, those carrying a gene that also outwardly express traits for that gene.
Phenotype	Manifestation of a genetic trait as a clinically observable sign or symptom.
Phlebotomy	To puncture a vein for the purpose of withdrawing blood. The preferred treatment for those suffering from hemochromatosis.
Porphyria cutanea tarda	Disorder of heme biosynthesis due to a defective liver enzyme (uroporphyrinogen decarboxylase). Symptoms include photosensitivity; hepatic dysfunction; discolored teeth, gums and skin; excessive hair; and psychiatric symptoms that result from porphyrin accumulation in the blood.
Prevalence	The percentage of cases of a disease in a population at a given time.
Recessive trait	A genetic disorder that appears only in patients who have two copies of a mutant allele, one from each parent. An individual who has one copy of the mutant allele is a carrier.
S65C mutation	A missense mutation that causes a cysteine to replace a serine at nucleotide position 193. The mutation is in a region implicated in binding the transferrin receptor to the HFE protein, and has a modest effect on iron metabolism. S65C has an allele frequency of 1.5% in the general population.
Secondary hemochromatosis	Acquired forms of hemochromatosis. Caused by various anemias, chronic transfusion therapy, or other non-genetic conditions.
Serum	Blood serum is the noncellular clear liquid that separates from blood on clotting. Serum is equivalent to plasma without plasma's clotting elements.
Serum ferritin test (SF)	Determines serum ferritin levels. The body increases production of serum ferritin when excess iron is absorbed. Normal levels are <200 ng/ml for premenopausal females, <300 for males and postmenopausal females.
Serum glutamic-oxaloacetic transaminase (SGOT)	A hepatic enzyme detected in blood tests and used in cases of suspected coronary occlusive heart disease, or liver diseases such as hepatitis or cirrhosis. A 2 to 3-fold increase in SGOT is found in 50-60% of patients with HHC (see AST).
Serum glutamic pyruvic transaminase (SGPT)	An enzyme released into the bloodstream due to injury or disease affecting the liver: it is found mainly in blood serum and hepatic tissues. SGPT levels are checked for suspected liver disease and mononucleosis, or to monitor the effect of long-term drug therapy on the liver (see

	ALT).
Sideroblastic anemia	Term used to describe a group of rare blood disorders characterized by the bone marrow's inability to manufacture normal red blood cells.
Tachycardia	Excessive rapidity in the action of the heart; the term is usually applied to a heart rate above 100 beats per minute.
Thalassemia	An inherited hemoglobin synthesis disorder resulting in reduced globin chain synthesis and chronic hemolytic anemia. Treating anemia by chronic transfusion therapy predisposes to secondary hemochromatosis.
Therapeutic phlebotomy	A procedure in which a unit of blood is collected via venipuncture to treat a condition such as iron overload.
Total iron binding capacity (TIBC)	Measurement of the maximum iron concentration that transferrin can bind. Increased TIBC levels may indicate iron-deficiency anemia; decreased TIBC may indicate cirrhosis (TIBC = UIBC + serum iron).
Transaminase	One of the aminotransferase enzymes, which catalyze the transfer of an amino group from an alpha-amino acid to an alpha-keto acid.
Transferrin	A protein synthesized in the liver that transports iron in the blood to red blood cells for use in heme synthesis.
Transferrin receptor, TfR	A transmembrane disulfide-linked dimer of identical 85-kDa polypeptides mediating iron uptake. The amount of transferrin receptor expressed on a cell is proportional to the cell's need for iron. Since the majority of metabolic iron is used for hemoglobin synthesis, 80% of total TfR is on erythroid precursor cells.
Transferrin saturation test (TS)	Proportion of transferrin proteins that are carrying iron. Normal range is 16%-45% in a fasting TS. Elevated TS indicates iron overloading.(serum iron [SI] / TIBC x 100) or (SI / SI + UIBC x 100).
Unsaturated iron binding capacity (UIBC)	About one third of transferrin iron-binding sites are occupied by iron; therefore, serum has considerable reserve iron-binding capacity. This is called serum unsaturated iron binding capacity (UIBC) (see TIBC).
Vibrio vulnificus	A microbe that causes food-poisoning-like symptoms.
Wild type	In genetics, the standard phenotype for any organism, or a gene that determines a standard phenotypic trait.

Glossary references

Discovering Nutrition

List and glossary of medical terms*

Medfriendly.Com

Medline Plus

National Human Genome Research Institute

NDI Foundation*

Principal Health News

R & D Systems
The Prostate Glossary*

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RESOURCES

Resources developed by the CDC to assist primary care providers inform hemochromatosis patients and their families include:

- **Phlebotomy information** for patients with hemochromatosis (pdf file)
- **Diet information** for patients with hemochromatosis (pdf file)
- **Talking with your family members** about hemochromatosis (pdf file)
- **Letter for patients** to give to their immediate family members (blood relatives) explaining family based detection. (pdf file)
- **CDC Brochure** "Iron Overload and Hemochromatosis: Information for patients and their families" (pdf file)
- **CDC Hemochromatosis web page**. includes downloadable patient brochure and frequently asked questions and answers.

These online resources are available to assist the primary care professional diagnose and treat patients who have iron overload, hemochromatosis, and hereditary hemochromatosis.

Phlebotomy information

- **AMA's Council on Scientific Affairs*** Report Blood Donation Recommendations
- **Iron Disorders Institute (IDI)***
- **NIH News Release:** Study Finds Hemochromatosis Patients' Blood is as Safe as Other Donated Blood: May Help Alleviate Blood Shortage
- **The American Red Cross*:** Learn more about blood donation opportunities*
- **The American Association of Blood Banks*:** Where to Donate and Receive Blood

Dietary supplements

- **NIH** – Facts about dietary supplements

Genetics

- **CDC Genetics and Disease Prevention Information** - resources on genetics, including journals, reports, and fact sheets. Includes online multimedia presentations ranging from basic genetics to latest research.
- **NIH – Frequently Asked Questions About Genetics**
- **NIH - Glossary of Genetics Terms**
- **Glossary of Basic Genetic Terms***
- **National Society of Genetic Counselors, Inc*.** ResourceLink at NSGC has been developed to assist consumers in locating genetic counseling services and for students curious about the profession. Genetic Counselors can be searched by State, City, Counselor's Name, Institution or Areas of Practice or Specialization.
- **Continuing Medical Education in Genetics*** - includes Core Educational Guidelines in Medical Genetics for family practice residents from the American Academy of Family Physicians.

Iron and hemochromatosis

- **CDC - Hemochromatosis web page**- includes downloadable patient brochure and frequently asked questions and answers.
- **CDC Anemia and Iron Status web page.** - includes a pdf version of Recommendations to Prevent and Control Iron Deficiency in the United States.
- **Iron Disorders Institute (IDI)*** - a national voluntary health agency that provides patient services, books, and literature about hemochromatosis and other disorders of iron such as non-*HFE* related iron overload, iron loading anemia, anemia of chronic disease, and iron deficiency anemia
- **American College of Physicians/American Society of Internal Medicine*,** Annals of Internal Medicine Supplement - Iron Overload, Public Health and Genetics.
- **MEDLINEPLUS** – a service of the National Library of Medicine provides links on iron overload and hemochromatosis including a link for ongoing hemochromatosis clinical trials.

Journals

- **Patient Education Handout*** – a handout for patients titled "Low serum ferritin level rules out advanced liver disease in hemochromatosis." This summary is published in Ann Intern Med. 2003 April 15; 138(8): I1.

- **PubMed** - a service of the National Library of Medicine provides access to more than 12 million MEDLINE citations from the mid-1960s forward, and other life science journals. Create your own reference search using PubMed/MEDLINE.

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Disclaimer

This Web site training course does not define a standard of care, nor is it intended to dictate an exclusive management course. Standards of medical care are determined on the basis of all the facts and circumstances involved in an individual case and are subject to change as scientific knowledge and technology advance and patterns evolve.

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- Search the catalogue and find the course, Hemochromatosis: What every clinician and health care professional needs to know.
- Follow instructions to select the type of continuing education credit you want and register for the course.
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- If you are not interested in receiving continuing education credit, we encourage you to complete the course evaluation. Your comments are valuable to us and we are very interested in receiving feedback from all participants. To do this, follow the instructions above and register for "Audit."

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