What every medical professional needs
to know about...

hemochromatosis

...early detection and treatment
saves lives.

According to the U.S. Centers for Disease Control and Prevention:
"More than one million people in the United States
have the gene mutations for hemochromatosis,
a leading cause of iron overload disease."

Iron Disorders Institute℠

promoting wellness through iron-balance

At-a-Glance Reference Charts

Content developed in part with resources cited below and with advise from members of the Iron Disorders Institute Scientific Advisory Board.

Methods to determine iron overload

Bloodwork

- Fasting serum iron
- Total iron binding capacity

→ serum iron÷TIBC x 100%= TS% (normal 25-35%)

- Serum ferritin: See ranges below

Procedures

- Liver biopsy with quantitative iron stain (used in some cases; especially those with normal TS% with elevated serum ferritin) For details, see diagnosis algorithm next page
- Quantitive phlebotomy For details, see diagnosis algorithm next page

TS%= transferrin-iron saturation percentage

Comparing disorders of iron

iron panel	IRON PANEL TESTS					
	Serum Iron	Serum Ferritin	Transferrin Iron Saturation Percentage	Total Iron Binding Capacity (TIBC)	Transferrin	Hemoglobin
Hemochromatosis	↑	↑	↑	↓	↓	NORMAL
Iron Deficiency Anemia	↓	↓	↓	↑	↑	↓
Sideroblastic Anemia	↑	↑	↑	↓	↓	↓
Thalassemia	↑	↑	↑	↓	↓	↓
Porphyria Cutanea Tarda (PCT)	↑	↑	↑	↓	↓	NORMAL
Anemia of Chronic Disease (ACD)	↓	↑ OR NORMAL	↓	↓	↓	↓
African Siderosis (AS)	↑	↑	↑	↓	↓	NORMAL
Vitamin B12 Deficiency (pernicious anemia)	↑ OR NORMAL	↑ OR NORMAL	↑ OR NORMAL	↓ OR NORMAL	↓ OR NORMAL	↓

ferritin

	Adult Males	Adult Females
Normal Range	up to 300 ng/mL	up to 200 ng/mL
In de-ironing treatment	below 100 ng/mL	below 100 ng/mL
Ideal maintenance	25-75 ng/mL	25-75 ng/mL

Adolescents, Juveniles, Infants & Newborns
of normal height and weight for weight and gender

Male ages 10-19 years 23-70 ng/mL	Infants 7-12 months 60-80 ng/mL
Female ages 10-19 years 6-40 ng/mL	Newborn 1-6 months 6-410 ng/mL
Children ages 6-9 years 10-55 ng/mL	Newborn 1-30 days 6-400 ng/mL
Children ages 1-5 years 10-55 ng/mL	

Ferritin ranges differ from lab to lab; ranges in this chart were established by consensus of the Iron Disorders Institute Scientific Advisory Board Members 1999.

Clinical Features of Patients with Hemochromatosis

There is a broad spectrum of features, ranging from total lack of symptoms to advanced liver, heart, joint or endocrine disease.

Following is a list of possible ways of identifying hemochromatosis in the asymptomatic patient:

- Abnormal serum iron studies on routine screening chemistry panel
- Evaluation of abnormal liver tests
- Identified by family screening
- Identified by population screening

Non-specific, systemic symptoms or complaints by the patient:

Weakness · Fatigue · Lethargy
Apathy · Weight loss

Specific Organ-related symptoms or diseases:

- Abdominal pain secondary to hepatomegaly
- Arthralgias (...especially reports of pain in the 2nd and 3rd metacarpophalangeal joints)
- Diabetes
- Amenorrhea
- Loss of libido, impotence
- Congestive heart failure, arrhythmias

Signs in the asymptomatic patient:

- Hepatomegaly

Signs in the symptomatic patient by system:

- Liver/Spleen/Gastrointestinal
  - Hepatomegaly
  - Cutaneous stigmata of chronic liver disease
  - Splenomegaly
  - Portal hypertension
  - Ascites
  - Esophageal varices
- Brain
  - Encephalopathy
- Joints
  - Arthritis (especially 2nd and 3rd metacarpophalangeal joints, knees, shoulders, and wrists)
  - Joint swelling
- Heart
  - Dilated cardiomyopathy
  - Congestive heart failure
- Skin
  - Increased pigmentation (bronze, ashen-gray)
- Endocrine
  - Testicular atrophy
  - Hypogonadism
  - Hypothyroidism

Adapted with permission: Journal of Hepatology
Source: Harrison, S.A, B. R. Bacon. Hereditary hemochromatosis: Update for 2003. Journal of Hepatology 38 (2003): S14-S23.

Mean Corpuscular Volume (MCV) Reference Ranges

Newborn: 95 to 121 fl
Ages 6 months to 2 years: 70 to 86 fl
Ages 12 to 18 years
Boys: 78 - 98
Girls: 78 - 102
Age over 18 years: 78 to 98 fl

hemoglobin

	Adult Males	Adult Females
Normal Range	13.5-17.5 g/dL	12.0-16.0 g/dL

Adolescents, Juveniles, Infants & Newborns
of normal height and weight for their age and gender

Age 6-18 years 10.0-15.5 g/dL	Age 2-6 mos 10.0-17.0 g/dL
Age 1-6 years 9.5-14.0 g/dL	Age 0-2 weeks 12.0-20.0 g/dL
Age 6 mos-1year 9.5-14.0 g/dL	Newborn 14.0-24.0 g/dL

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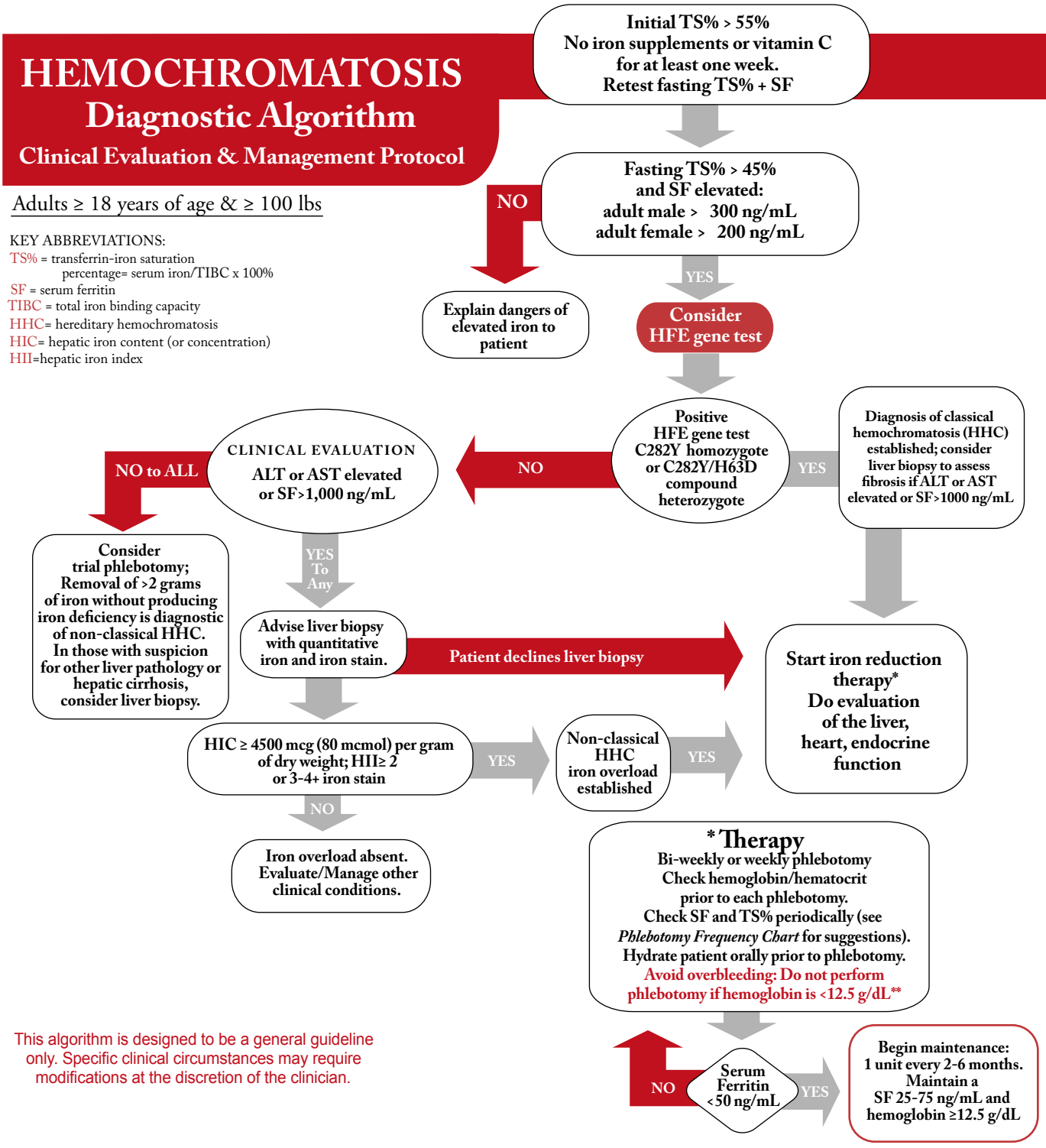
HEMOCHROMATOSIS
Diagnostic Algorithm
Clinical Evaluation & Management Protocol

Adults ≥ 18 years of age & ≥ 100 lbs

KEY ABBREVIATIONS:
TS% = transferrin-iron saturation percentage= serum iron/TIBC x 100%
SF = serum ferritin
TIBC = total iron binding capacity
HHC= hereditary hemochromatosis
HIC= hepatic iron content (or concentration)
HII=hepatic iron index



This algorithm is designed to be a general guideline only. Specific clinical circumstances may require modifications at the discretion of the clinician.

**Exceptions to pre-treatment hemoglobin of 12.5 g/dL include females, whose normal hemoglobin range begins at 12.0 g/dL. Other exceptions include patients with cirrhosis or other disorders such as sideroblastic anemia. The intent is to avoid unnecessary over-bleeding and symptoms of iron deficiency anemia. Serum ferritin should be maintained within normal limits. There is no known health benefit to below normal SF.

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Phlebotomy Frequency Guidelines

For iron overload in adults without anemia

Hgb/Hct (hemoglobin/hematocrit)	SF (serum ferritin)	TS% (transferrin-iron saturation percentage)	MCV (mean corpuscular volume of red blood cells)	Iron Reduction & Management	
Normal	Elevated 1,000 ng/mL or greater	Elevated greater than 45%	Normal	Aggressive	One (500cc) or two units per week (depending upon initial SF and alcohol consumption)until SF is lowered to <750 ng/mL; check SF & TS% initially in 4-6 weeks; thereafter 3-6 mos.

Important: serum ferritin (SF)>1,000 ng/mL increases the risk of cirrhosis and liver cancer.
The risk of cirrhosis is <1% in patients whose SF has not been elevated above 1,000 ng/mL.

Hgb/Hct	SF	TS%	MCV	Management	
Normal	Elevated above Normal see ferritin reference	Elevated	Normal	Aggressive to Moderate	One unit (500cc) per week depending upon patient, may need to adjust to one unit every other week. Check SF & TS% initially in 4-6 weeks; thereafter 3-6 mos.
Normal	High Normal see ferritin reference	**Elevated greater than 45%**	Normal	Moderate	One unit (500cc) monthly. Check SF & TS% 3-6 mos.
Normal	Normal see ferritin reference	Normal 25-35%	Normal	Maintenance	One unit (500cc) periodically, to maintain serum ferritin 25-75 ng/mL with TS% <45% Check SF & TS% 6 mos to annually.
Normal	Elevated see ferritin reference	Normal	Normal	Rule out non-alcoholic steatohepatitis (NASH), chronic liver disease (alcohol, hepatitis) or hyperferritinemia cataract syndrome (HFC). NASH diagnosis includes: hyperinsulinemia + hepatic iron index <1.9 HFC diagnosis: opthalamologist confirms early onset cataracts. HFC is not a condition of iron overload.	
Normal	Normal	Elevated	Normal or slightly Decreased	Iron avidity is a common phenomenon for hemochromatosis patient, possibly caused by abnormal shuttling of iron into plasma due to genetic makeup of the patient or a physiological response to chronic blood loss and diet modifications. **Discontinue phlebotomies,** check SF & TS% in 3-6 mos. resume phlebotomy when SF is >55ng/mL.	
Below or Low Normal (10.5 to 12.0g/dL)	Normal or below Normal	Normal or below Normal	Normal or slightly Decreased	Rule out Anemia of Chronic Disease (ACD). Treat underlying condition: i.e., infection, arthritis, inflammatory bowel disease, etc. Check for fever.	
Below or Low Normal (10.5 to 12.0g/dL)	Elevated or Normal	Elevated or Normal	Elevated	Rule out B12/folic acid deficiency with serum B12, folate and/or serum or urine methylmalonic acid (MMA & UMMA) and homocysteine	

Charts provide general guidelines only.
Specific clinical circumstances may require modifications at the discretion of the clinician.

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Phlebotomy Options

Charts provide general guidelines only. Specific clinical circumstances may require modifications at the discretion of the clinician.

Treatment for iron overload in those who do not have concurrent anemia is therapeutic phlebotomy. Most patients are candidates for standard phlebotomy. **Patients should have a pre-treatment hemoglobin ≥12.5g/dL*.** Quantities removed by phlebotomy can vary from minimal extraction of 250cc up to large volume extraction of 600cc. Extraction continues until serum ferritin reaches 25ng/mL on one occasion but hemoglobin does not drop below normal range for age, weight or gender.

	TYPE OF PHLEBOTOMY			
	STANDARD	**MINIMAL VOLUME**	**LARGE VOLUME**	
Procedure	Extracted from a vein, typically the arm, using a 16 gauge needle (same as volunteer blood donation; except order is required)	Extracted from a vein typically the arm using a 20-22 gauge butterfly needle & vacuum bag	Chest port surgically implanted near collar bone area	Double red cell apheresis (DRCA)
Patient Profile & Eligibility	Most patients who weighs more than 110 lbs and whose hemoglobin is ≥ 12.5g/dL	For youths, persons who are frail, small in stature or weight (less than 100 lbs) or who have coexistent illness such as heart problems*	Uncommon; used in rare cases for adults of normal weight with vein access problems or other medical complications	Hemochromatosis patients who meet elegibility requirements: hemoglobin 13.3g/dL and body proportions: Males: 5'1"; 130 lbs Females: 5'5"; 150 lbs
Duration of Procedure	~15-20 minutes	~15-20 minutes	~15-20 minutes	~40 minutes
Volume Blood Removed	~450-500 cc of blood	~200-250 cc of blood	~600 cc of blood	~360 mL Packed Red Cells
Iron Removed	~ 250 mgs	~125 mgs	~300 mgs	~410 mgs
Comments	Most common problems reported are underbleeding or overbleeding the patient. To lower the risk of these consequences, refer to the Phlebotomy Frequency Guidelines Chart.	Frequency may be increased depending on patient tolerance. *patient may have small, inaccessible, scarred or rolling veins *patient may be unable to tolerate standard volume of blood removal	Serious procedure not to be considered a routine option	DRCA is a nice option to offer HHC subjects, since it halves the number of visits to the blood center, while accomplishing nearly the same degree of iron removal. DRCA is well tolerated with few side effects, such as tingling sensation as plasma and citrate anti-coagulant are returned to the body.

TS% = Transferrin-Iron Saturation Percentage= Serum iron/TIBC X 100%

SF = Serum Ferritin

TIBC = Total Iron Binding Capacity

*Sample Phlebotomy Order

"Phlebotomize 500 cc once a week** if Hgb ≥12.5g/dL"
(Approximate hematocrit of 38%)
**period of time should reflect frequency desired

For a **Double Red Blood Cell Apheresis** order suggestions visit:

www.**irondisorders**.org

IMPORTANT NOTES:

1. Pre-treatment Hgb ≥ 12.5g/dL for most.
2. Serum ferritin (SF) and transferrin iron saturation percentage (TS%) should be checked periodically; see Phlebotomy Frequency Chart for suggestions. A complete blood count (CBC) may done at this time to determine MCV, etc.
3. MCV will drop by 3% of baseline without causing anemia when de-ironing is achieved.
4. Some patients undergoing phlebotomy may need fluid replacement.
5. **DRCA requirements:** Women have smaller circulating blood volumes than men. However, the machine removes the same volume no matter what the donor gender. Therefore, to increase safety to donors, women have to be larger. Larger women have the same circulating blood volume as smaller men.
6. For patients whose initial serum ferritin is ≥1,000 ng/mL, SF should be evaluated in 4-6 weeks until SF is lowered to <750ng/mL. Thereafter, SF can be checked in 3-6 months to determine the patient's unloading pattern. A complete blood count is also recommended during these routine evaluations.
7. Pharmacological removal of iron with desferioxamine or deferasirox may be considered in cases where phlebotomy cannot be tolerated or may be used as an adjunct to phlebotomy. This would currently be off-label use of these drugs.
8. **Treatment Centers:** The US FDA has granted variances to private blood centers and The American Red Cross that allows hemochromatosis (HHC) blood to be used for transfusional purposes. The HHC blood is screened in exactly the same way as routine donor blood. Most centers with this special variance offer treatment free of charge to HHC patients; a physician's order is required. See sample order on this page.

Contact Iron Disorders Institute for the nearest center accepting HHC patients for therapeutic phlebotomy. Any HHC patient who lives near Bethesda, MD may wish to contact The Warren G. Magnuson Clinical Center, Hemochromatosis Protocol Coordinator, Yu Ying Yau, RN, at 301-496-1430. Or email: yyau@mail.cc.nih.gov

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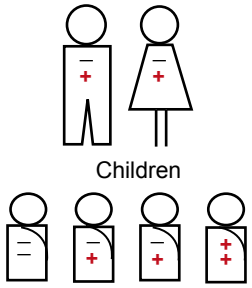
Examples of *HFE* Genotypes in Families with Hemochromatosis

Homozygote: inherits two copies of the same mutated *HFE* gene.
Heterozygote: inherits one copy of a mutated *HFE* gene. Also called a carrier.
Compound Heterozygote: inherits two different mutated copies of the *HFE* gene.

GENE MUTATIONS • Homozygote • Heterozygote • Compound Heterozygote

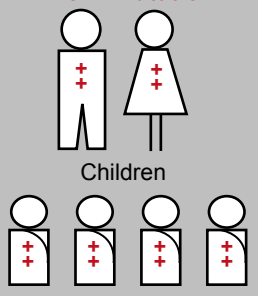
– Normal or Unknown Mutation **+ C282Y Mutation** **▲ H63D Mutation**

Both Parents Heterozygous for C282Y Mutation



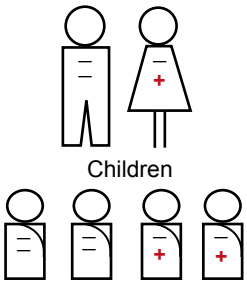
25% chance: Normal
50% chance: C282Y Carrier
25% chance: C282Y Homozygote

Both Parents Homozygous for C282Y Mutation



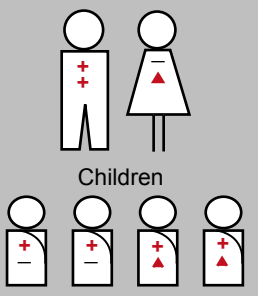
100% chance: C282Y Homozygote

One parent normal Other Heterozygous C282Y Mutation



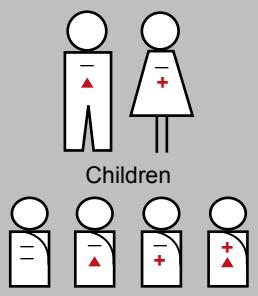
50% chance: Normal
50% chance: C282Y Carrier

One Parent is Heterozygous for H63D Mutation. One is a Homozygous for C282Y Mutation



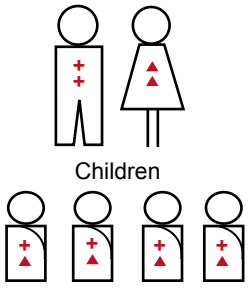
50% chance: C282Y Carrier
50% chance: Compound Heterozygote

Both Parents are Heterozygous for Different Mutations



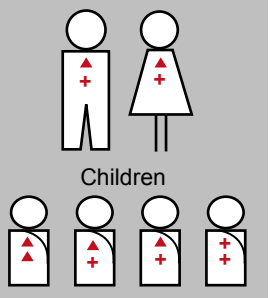
25% chance: Normal
25% chance: H63D Carrier
25% chance: C282Y Carrier
25% chance: Compound Homozygote

Both Parents Homozygous Different Mutations



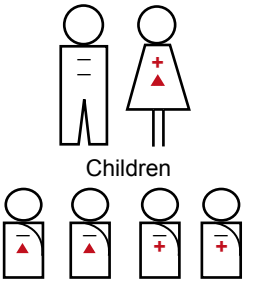
100% chance:
Compound Heterozygote

Both Parents Compound Heterozygotes



25% chance: H63D Homozygote
50% chance: Compound Heterozygote
25% chance: C282Y Homozygote

One Parent Normal One Parent Compound Heterozygote



50% chance: H63D Carrier
50% chance: C382Y Carrier

IMPORTANT NOTES:

- The inheritance pattern of classical (Type I) Hemochromatosis is autosomal, recessive
- Everyone inherits two copies of HFE
- Mutated copies of HFE are found primarily in Caucasians
- Only the mutated copies C282Y and H63D are represented in this chart because these are the most important known mutations to date
- When one parent has two mutated copies of HFE, all offspring are at least obligate carriers
- HFE mutations are present in about 85% of Caucasians in the USA with hereditary hemochromatosis
- HFE related iron overload is an adult onset disorder. Other genes that can cause iron overload in children are not included in this chart
- The risk of iron loading is presently known to be greatest in men who are C282Y homozygotes
- Heterozygotes, especially compound heterozygotes are also at increased risk of iron loading, but likelihood and severity are lower
- Informed consent: Anyone considering genetic testing should be made aware of the potential consequences, such as possible insurance and employer discrimination or paternity identification
- Genetic status provides no information about tissue iron levels. Clinical evaluation of serum ferritin and transferrin iron saturation percentage is one way to estimate tissue iron status
- For more information about prevalence and penetrance of HFE, contact Iron Disorders Institute: info@irondisorders.org

Diet Recommendations for Hemochromatosis

Normally people absorb about 1 milligram of iron per day to meet body needs. Individuals with hemochromatosis can absorb from the small intestines as much as four times that amount. The body has no way of ridding itself of the extra iron. Over time the extra iron accumulates in vital organ such as the liver, joints, heart, pancreas and the pituitary resulting in disease.

For this reason, individuals with hemochromatosis must take steps to reduce the level of body iron with therapeutic phlebotomy and control iron absorption with diet modifications.

We consume two types of iron from the diet: iron in heme contained in meat and non-heme iron contained in plants and supplements. Heme iron is most easily absorbed, whereas non-heme is absorbed less well. Calcium is the only known substance that can impair the absorption of both heme and non-heme iron. Tannin (coffee, tea, chocolate), fiber, eggs and oxalates impair absorption of non-heme iron.

Ask for the Iron Disorders Institute recommendation guidelines for diagnosing, treatment inheritance patterns and DNA testing for individuals at risk for hemochromatosis.

The following recommendations are suggestions to modify the diet for individuals with hemochromatosis. Every person is unique, which must be taken into consideration before using some of these suggested diet modifications. People with liver disease especially need to be cautious about consumption of certain foods or substances.

- **Reduce consumption of red meat**
  Red meat contains the most easily absorbable form of iron called heme iron.
- **Avoid foods high in animal fats**
  Fats (lipids) when in combination with unbound iron can generate free radical activity, which is destructive to cells and can damage DNA.
- **Limit supplemental vitamin C to 200 milligrams/dose**
  Vitamin C enhances iron absorption.
- **If alcoholic beverages are allowed, consume in moderation**
  Alcohol enhances the absorption of iron
  Too much alcohol can damage the liver
  Red wine can be of benefit when consumed in moderation because of the tannins it contains.
  Patients with elevated liver enzymes or liver damage such as cirrhosis should avoid alcohol completely.
- **Avoid sugary foods or beverages**
  Sugar enhances the absorption of iron.
- **Consume plenty of fruits and vegetables, including spinach**
  These foods contain fiber and antioxidants, which inhibit free radical production. Spinach contains oxalates which impair absorption of iron contained in this plant. Fruits and vegetables contain non-heme iron which is not absorbed well.
- **Eat nuts, grains, rice and beans**
  These foods are high in fiber, which impairs the absorption of non-heme iron and promote healthy digestion.
- **Avoid raw shellfish if iron levels are elevated**
  Shellfish can contain a bacterium called *Vibrio vulnificus*, which can be fatal to people with high body iron levels. Take care when walking barefoot on beaches where contaminated shells may be present.
- **Tea or coffee with meals can reduce the absorption of iron**
  These beverages contain tannins which inhibit the absorption of non-heme iron. Excessive consumption of tannins is not recommended for individuals with liver damage.

IRON
content in select types of meat & fish

	per 3.2 oz serving		
	total iron MILLIGRAMS	heme iron MILLIGRAMS	heme iron percentage of total iron
VENISON	4.5	2.3	51
LAMB	3.1	1.7	55
BEEF			
RUMP STEAK	2.9	1.5	52
SIRLOIN STEAK	2.5	1.3	52
ROUND STEAK	3.2	1.6	50
TOP ROUND	2.5	1.2	48
GROUND	2.5	1.0	40
BRISKET	2.0	0.5	25
VEAL			
PORK	1.3	0.3	23
PROCESSED MEATS			
SAUSAGE (VEAL)	0.7	0.0	0.0
BOILED HAM	0.7	0.0	0.0
LIVER PATE	5.0	0.8	16
CHICKEN	0.6	0.0	0.0
FISH			
COD	0.2	0.0	0.0
MACKEREL	0.7	0.0	0.0
SALMON	0.6	0.1	17
MUSSELS	4.6	2.2	48
LOBSTER	1.6	0.6	40
SHRIMP	2.6	1.0	40

Meat contains about 40-50% heme iron; the balance is non-heme. The iron in plant-based foods is nearly all non-heme iron, but some plants do have traces of heme iron. These plants are not commonly consumed by humans.

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For a complete list of iron content in foods visit www.irondisorders.org

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*"**Early detection** of iron overload disease represents a major chronic desease prevention opportunity. Detection and treatment (phlebotomy) of iron overload, early in the course of the illness, can substantially reduce the severity of symptoms, organ damage, and death from associated chronic diseases."*

David Satcher, M.D., Ph.D.,
Former Assistant Secretary for Health and US Surgeon General

Physicians

Contact us for information about participating in our Physician's Registry

Direct your patients to our website
www.irondisorders.org

and to our book
Iron Disorders Institute Guide to Hemochromatosis
Cumberland House Publishing 2001

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Iron Disorders Institute
promoting wellness through iron-balance

Contact us for other REFERENCE CHARTS:
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OUR MISSION:
Iron Disorders Institute (IDI) exists so that people with iron disorders receive early, accurate diagnosis, appropriate treatment and are quipped to live in good health.

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