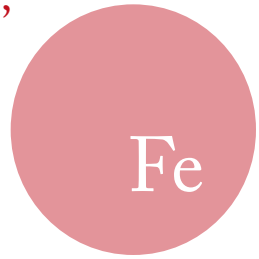
What every medical professional will
want to know about...

hemochromatosis

...early detection and treatment
saves lives.

According to the U.S. Centers of 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."



At-a-Glance Reference Charts

Key abbreviations:

HHC=hemochromatosis
HIC=hepatic iron content (or concentration)
HII=hepatic iron index (HIC/age in years)
TIBC=total iron-binding capacity
TS%=transferrin-iron saturation percentage
SF=serum ferritin

Other abbreviations:

ALT: serum alanine aminotransferase
AST: serum aspartate aminotransferase
HFC=hyperferritinemia cataract syndrome
Hgb/Hct=hemoglobin/hematocrit
MCV=mean corpuscular volume of red blood cell
NASH=non-alcoholic steatohepatitis

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

Tests: to determine iron overload

Fasting serum iron / Total iron binding capacity → serum iron÷TIBC x 100%= TS% (normal 25-35%)

Serum ferritin: See Ferritin Chart below for ranges

Liver biopsy with quantitative iron stain (used in some cases; especially those with normal TS% with elevated serum ferritin)

Hepatic Iron Content (HIC)≥ 4500 mcg (80 mcmol) per gram of dry weight or 3-4+ iron stain or HII≥2

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www.irondisorders.org
Go to Resources

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	

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	14.0-18.0 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= hemochromatosis

HIC= hepatic iron content (or concentration)

HII=hepatic iron index

Initial TS% > 55%
No iron supplements or vitamin C for at least one week.
Retest fasting TS% + SF

Fasting TS% > 45% and SF elevated:
adult male > 300 ng/mL
adult female > 200 ng/mL

NO → Explain dangers of elevated iron to patient

YES → Consider HFE gene test

Positive HFE gene test C282Y homozygote or C282Y/H63D compound heterozygote

YES → Diagnosis of classical hemochromatosis (HHC) established; consider liver biopsy to assess fibrosis if ALT or AST elevated or SF>1000 ng/mL → Start iron reduction therapy* Do evaluation of the liver, heart, endocrine function

NO → CLINICAL EVALUATION
ALT or AST elevated or SF>1,000 ng/mL

NO to ALL → Consider trial phlebotomy; Removal of >2 grams of iron without producing iron deficiency is diagnostic of non-classical HHC. In those with suspicion for other liver pathology or hepatic cirrhosis, consider liver biopsy.

YES To Any → Advise liver biopsy with quantitative iron and iron stain.

Patient declines liver biopsy → Start iron reduction therapy* Do evaluation of the liver, heart, endocrine function

HIC ≥ 4500 mcg (80 mcmol) per gram of dry weight; HII≥ 2 or 3-4+ iron stain

YES → Non-classical HHC iron overload established → YES → Start iron reduction therapy* Do evaluation of the liver, heart, endocrine function

NO → Iron overload absent. Evaluate/Manage other clinical conditions.

***Therapy**
Bi-weekly or weekly phlebotomy
Check hemoglobin/hematocrit prior to each phlebotomy.
Check SF and TS% periodically (see *Phlebotomy Frequency Chart* for suggestions).
Hydrate patient orally prior to phlebotomy.
Avoid overbleeding: Do not perform phlebotomy if hemoglobin is <12.5 g/dL**

Serum Ferritin <50 ng/mL
NO → Therapy
YES → Begin maintenance: 1 unit every 2-6 months. Maintain a SF 25-75 ng/mL and hemoglobin ≥12.5 g/dL

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

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

Hgb/Hct (hemoglobin/hematocrit)	SF (Serum Ferritin)	TS% (transferrin-iron saturation percentage)	MCV (mean corpuscular volume of red blood cells)	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 greater than 45%	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	

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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"

**period of time should reflect frequency desired

For a
Double Red Blood Cell Apheresis
sample order
contact Iron Disorders Institute
info@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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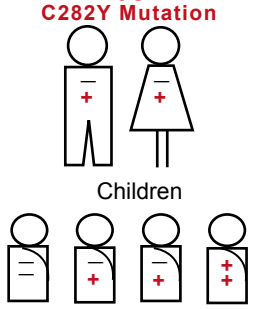
Examples of *HFE* Genotypes in Families with Hemochromatosis

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

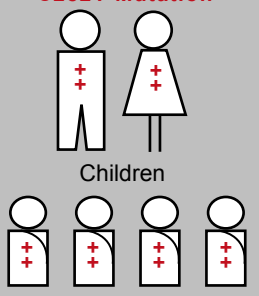
— Normal or Unknown Mutation **+ C282Y Mutation** **▲ H63D Mutation**

Both Parents Heterozygous for C282Y Mutation



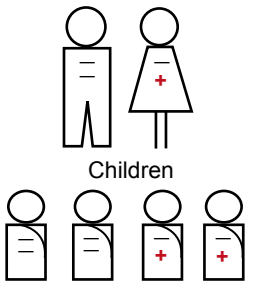
25% chance: Normal
50% chance: C282Y Carrier
25% chance: C282Y Homozygote

Both Parents Homozygous for C282Y Mutation



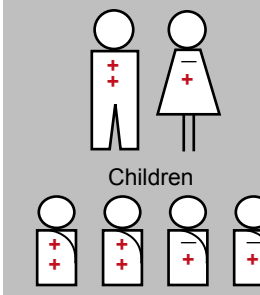
100% chance: C282Y Homozygote

One parent normal Other Heterozygous C282Y Mutation



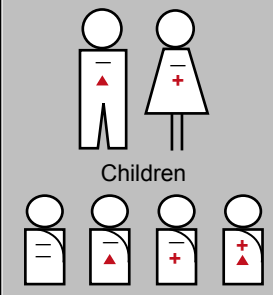
50% chance: Normal
50% chance: C282Y Carrier

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



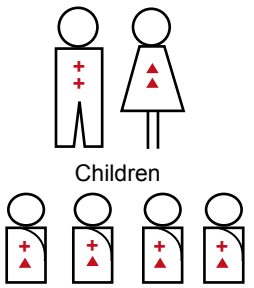
50% chance: C282Y Carrier
50% chance: C282Y Homozygote

Both Parents are Heterozygous for Different Mutations



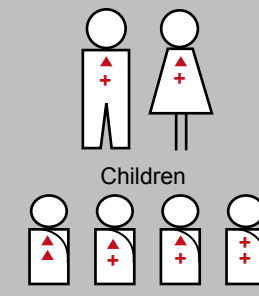
25% chance: Normal
25% chance: H63D Carrier
25% chance: C282Y Carrier
25% chance: Compound Homozygote

Both Parents Homozygous Different Mutations



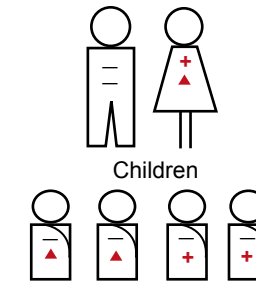
100% chance:
Compound Heterozygote

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: C282Y 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

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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.

Sources: Hallberg L, Hulthen L, Prediction of Dietary Iron Absorption: An Algorithm for Calculating Absorption and Bioavailability of Dietary Iron. *American Journal of Clinical Nutrition* 2000, 71: 1147-60.
The American Dietetic Associations' Complete Food & Nutrition Guide, 2nd ed. 2002
USDA National Nutrient Database

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

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

Contact Iron Disorders Institute

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Contact us for other
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888-565-4766

Preventing disease caused by Iron-Out-of-Balance™

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The purpose of Iron Disorders Institute (IDI) is to aid in the prevention and treatment of disease caused by Iron-Out-of-Balance™. IDI develops and distributes without charge evidence-based literature about iron and iron-related disorders; partners strategically with other voluntary and government health agencies to raise awareness about iron as a risk factor for many diseases; and advocates for all afflicted patients, including those newly diagnosed, underserved, in pain, or suffering the loss of a loved one due to an iron-related death.

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