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Hemochromatosis

Hemochromatosis is an inheritable condition that mainly affects White populations of European descent. Most patients remain asymptomatic, but others develop advanced organ damage that reduces quality of life and long-term survival. Arthropathy, diabetes mellitus, cirrhosis, hypogonadotropic hypogonadism, and cardiomyopathy are key clinical manifestations. Primary care and hospital medicine physicians play an essential role in early identification of this disease, which can be accomplished via standard hematologic testing. Early diagnosis and therapeutic phlebotomy improve clinical outcomes.

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Epidemiology and Screening

What is hemochromatosis, and what are its clinical manifestations?

Hemochromatosis is a common inheritable metabolic disorder in White populations of European descent, characterized by increased intestinal absorption and accumulation of iron in various organs, particularly the liver. Hemochromatosis can be classified (1) as *HFE* gene–associated (which is the more common and clinically relevant form) or non–*HFE*-associated (2, 3). The *HFE*-related form is commonly due to p.C282Y homozygosity (autosomal recessive) and is found in approximately 80% of patients with this condition (4); it affects approximately 1 in 200 people and presents most commonly in the fourth or fifth decade of life, although this varies within subpopulations of European ancestry (5).

The iron overload causes deposits in joints and organs, such as the endocrine system, liver, or heart, but clinical presentation may range from asymptomatic laboratory abnormalities to overt clinical disease (6). The first hematologic manifestations of hemochromatosis consist of elevations in serum transferrin saturation, elevations in mean red cell hemoglobin level, and macrocytosis, followed by high serum ferritin levels (7). In overt cases, hemochromatosis may present with arthritis; diabetes mellitus, pituitary insufficiency, and other endocrinopathies and hormonal deficiencies; liver fibrosis, including cirrhosis and hepatocellular carcinoma (HCC); cardiac manifestations, including heart failure and arrhythmias; and hyperpigmentation.

Early treatment by reducing iron overload through therapeutic phlebotomy and other approaches improves long-term outcomes and decreases risk for cirrhosis and liver cancer. The 2019 American College of Gastroenterology (ACG) guidelines (3) and the 2022 European Association for the Study of the Liver (EASL) guidelines (2), which informed this review, provide recommendations on identification and management of hemochromatosis based on a systematic review of the evidence.

What causes hemochromatosis, and who is at risk?

Hemochromatosis is caused by genetic variants primarily in the *HFE* gene that affect intestinal iron absorption and iron metabolism. Variants in other genes exist but are rare and have low clinical penetrance. The most common *HFE*-associated genotype that manifests disease is homozygosity for the p.C282Y variant (p.C282Y/C282Y), which comprises 80% of all cases. The variant leads to impaired synthesis of hepcidin, a small peptide made by the liver. Hepcidin exerts negative feedback on ferroportin, a transmembrane iron exporter, and consequently reduces both intestinal absorption of iron and release of iron by senescent erythrocytes in the spleen. Approximately 18.3% of patients with the homozygous p.C282Y variant have an associated elevation in liver enzyme levels.

Two other less common *HFE*-associated variants are the compound heterozygotes p.C282Y/H63D and p.C282Y/S65C. The H63D variant has a weaker effect on hepcidin. People with heterozygous p.C282Y/H63D form have less than a 5% risk for elevation in liver enzyme levels unless cofactors of liver disease, such as viral hepatitis or alcohol use disorder, are present (8). The risk for iron overload associated with p.H63D homozygous status (p.H63D/H63D) is even lower. Homozygosity for p.H63D is present in approximately 3% of the European population and is believed to account for fewer than 1% of cases of hemochromatosis. Thus, unlike the other 3 more prevalent variants (p.C282Y/C282Y, p.C282Y/H63D, and p.C282Y/S65C), guidelines for follow-up in patients with p.H63D homozygosity are not well established. Carrier states (wt/p.C282Y, wt/p.H63D, wt/p.S65C) are not typically associated with disease (3).

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HFE-associated hemochromatosis is much less prevalent in Hispanic (0.027%), Black (0.014%), and Asian (0.000039%) persons than in Northern European persons (0.44%) (9). Males are clinically affected 2 to 3 times more often than females. In women, clinical manifestations may occur at a later age as menstrual loss of iron provides protection.

Non–*HFE*-associated hemochromatosis is less common and includes several identified but uncommon variants and additional undiscovered variants (10, 11). These genetic conditions include those associated with variants of hemojuvelin (HJV), hepcidin antimicrobial peptide (HAMP), transferrin receptor 2 (TfR2) variants, and ferroportin (SLC40A1). Ferroportin variant is inherited in an autosomal dominant pattern, which is unique compared with the others identified. Next-generation and whole-genome sequencing has allowed for more granular evaluation of patients with iron overload (12, 13), including the HJV variant, which has poorly understood mechanisms and presents in adults younger than 30 years, and the TfR2 variant, which reduces hepcidin gene expression and has a clinical presentation similar to that in patients with p.C282Y/C282Y hemochromatosis. Ferroportin resistance to hepcidin has also been described. In approximately 10% of hemochromatosis cases, no known genetic variants are identified (11).

Hemochromatosis as a genetic disorder must be distinguished from secondary iron overload caused by hematologic and liver conditions, as phlebotomy is neither indicated nor beneficial in patients with iron overload not related to hemochromatosis (see the Diagnosis section).

What is the prognosis for patients with hemochromatosis?

Early identification and prevention of iron overload leads to outcomes largely matching those in the general population (3). Eighteen percent of men and 5% of women with *HFE*-associated hemochromatosis develop hepatic fibrosis (stage II to IV) yet remain asymptomatic during their lifetime despite hepatic iron overload (3, 14). Although people with p.C282Y homozygosity are more likely to have disease manifestations, prognosis and survival in patients without cirrhosis are similar to those with other *HFE* and non-*HFE* variants, with patients experiencing modest elevations in iron levels but rarely clinical hemochromatosis (15).

The Melbourne Collaborative Cohort Study of nearly 32 000 patients of northern European descent aged 40 to 69 years showed that over a 12-year period of clinical and biochemical data, approximately 29% of men with p.C282Y/C282Y homozygosity developed symptomatic iron overload (most commonly presenting with fatigue and joint pain) compared with 1.2% of women (16). Patients with hemochromatosis are 20 to 200 times more likely to develop primary liver cancer, which accounted for about 50% of deaths in this population (17).

Nongenetic risk factors, including age at diagnosis, sex, alcohol consumption, and diabetes, may contribute to the development and progression of clinical disease (6) (see the **Box**: Predictors of Poorer Prognosis in Hemochromatosis). Older age at diagnosis is associated with severity of disease, likely due to more prolonged exposure to high iron levels (18). Men develop earlier and more severe presentations, perhaps related to the suppressive effect of testosterone on hepcidin. Alcohol may have an inhibitory action on hepcidin and increase serum ferritin levels, which interferes with assessment of iron burden. Diabetes is not only a clinical

Predictors of Poorer Prognosis in Hemochromatosis

- Male sex
- Older age at presentation
- Alcohol consumption
- Type 2 diabetes mellitus
- Homozygous p.C282Y genetic variant

9. Adams PC, Reboussin DM, Barton JC, et al; Hemochromatosis and Iron Overload Screening (HEIRS) Study Research Investigators. Hemochromatosis and iron-overload screening in a racially diverse population. N Engl J Med. 2005;352:1769-1778. [PMID: 15858186]
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outcome but also a predictor of liver disease progression and decreased survival, presumably because of insulin resistance and metabolic dysfunction–associated steatotic liver disease (MASLD) (6). Although patients with p.C282Y homozygosity have a generally favorable prognosis, some studies indicate that these patients, particularly men, have increased risk for sarcopenia, frailty, chronic pain, and neurocognitive decline compared with people with non-*HFE* variants (19, 20).

Who should be screened for hemochromatosis, and what test should be used?

Major clinical guidelines do not support screening of the general population (2, 3). Some experts advocate 1-time biochemical screening with transferrin saturation and ferritin in White men aged 18 years or older (21), particularly those of Northern European ancestry and those with liver disease, chondrocalcinosis, or porphyria cutanea tarda due to the higher prevalence in these populations (22). However, the cost-effectiveness of this approach is uncertain. The main arguments against screening relate to the low clinical penetrance of the p.C282Y genotype and its variable prevalence among different ethnic groups (23). Screening of women is not recommended because they rarely develop cirrhosis or liver cancer; however, some groups have expressed concern about not screening women (24).

If both serum transferrin saturation and serum ferritin levels are elevated, genetic testing for the 3 most common *HFE* variants (p.C282Y/C282Y, p.C282Y/H63D, and p.C282Y/S65C) should be done (see the Diagnosis section). *HFE* gene testing should also be considered in patients with first-degree family members with any known *HFE* variants, even if serum iron levels are normal (3). Most homozygous relatives of probands develop biochemical and clinical manifestations of hemochromatosis because of their shared genetic abnormality and environment (25). Screening may be deferred until adulthood (age ≥18 years) as hemochromatosis rarely manifests before then.

Epidemiology and Screening... Hemochromatosis is a common inheritable disease that is typically transmitted in an autosomal recessive pattern, particularly in populations of Northern European origin. Most patients are asymptomatic, but men with p.C282Y homozygosity have the highest risk for clinical expression. Long-term prognosis is worse in men with p.C282Y homozygosity, people with diabetes, and those with non-*HFE* liver disease. Screening of men (aged ≥18 years) of European descent as well as first-degree relatives of the proband may be considered.

CLINICAL BOTTOM LINE

Diagnosis

What should the history and physical examination of a patient with suspected hemochromatosis include?

Although most patients are asymptomatic, the most common clinical manifestations of hemochromatosis include arthropathy; diabetes mellitus; cirrhosis; hypogonadotropic hypogonadism; cardiomyopathy; and, in later stages, decompensated cirrhosis, impotence, skin changes, infertility, cardiac arrhythmias, and heart failure (22) (**Table 1**). Thus, the history and physical examination should focus on signs and symptoms consistent with these manifestations.

Symptoms may include joint pain and stiffness; polyuria, polydipsia, peripheral neuropathy, or vision changes suggestive of hyperglycemia or diabetes

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Table 1. **Clinical Manifestations of Hemochromatosis**

Manifestation	*Assessment and Monitoring*
Joint (peripheral arthritis, arthralgias, spinal arthritis)	Radiographic imaging of symptomatic joints Standard symptom management with medications and therapies used in osteoarthritis Variable improvement with phlebotomy
Liver (elevated liver enzymes, hepatomegaly, hepatic fibrosis, cirrhosis, primary liver cancer)	Routine vaccination Evaluation with hepatic elastography Screening and interventions for other viral, autoimmune, and metabolic causes of chronic liver disease In cirrhotic patients, routine liver cancer screening; monitoring for complications of portal hypertension; and education on lifestyle modification, including alcohol abstinence
Cardiac (conduction abnormalities, myocardial siderosis, heart failure)	Consideration of baseline electrocardiogram for evaluation of tachyarrhythmias or nodal impairments Consideration of baseline echocardiogram to assess for signs of ventricular strain
Endocrine (hypogonadism, hypothyroidism, diabetes mellitus, hypopituitarism)	Consideration of baseline screening for endocrine dysfunction Standard follow-up for age-appropriate and risk factor–related routine care
Skin (hyperpigmentation)	No specific increase in risk for skin cancer is noted related to hemochromatosis-associated hyperpigmentation

mellitus; pituitary disturbance and loss of libido; and palpitations, shortness of breath, edema, fatigue, and lightheadedness indicative of cardiac involvement. A detailed review of the family history for unexplained cardiac or hepatic failure is important given the autosomal recessive inheritance of *HFE*-associated hemochromatosis.

The physical examination should evaluate for arthritis of the hands, although hemochromatosis may also affect large joints and the spine. Hemochromatosis-related arthritis typically affects the second and third metacarpophalangeal joints ("iron fist"), and plain radiographs may show "hook osteophytes." Siderosis of pancreatic islet is rare but may present as diffuse hyperpigmentation manifesting as "bronzing" of the skin. Classic findings of new-onset decompensated cirrhosis (ascites, hepatic encephalopathy, or portal hypertensive bleeding) should prompt further testing.

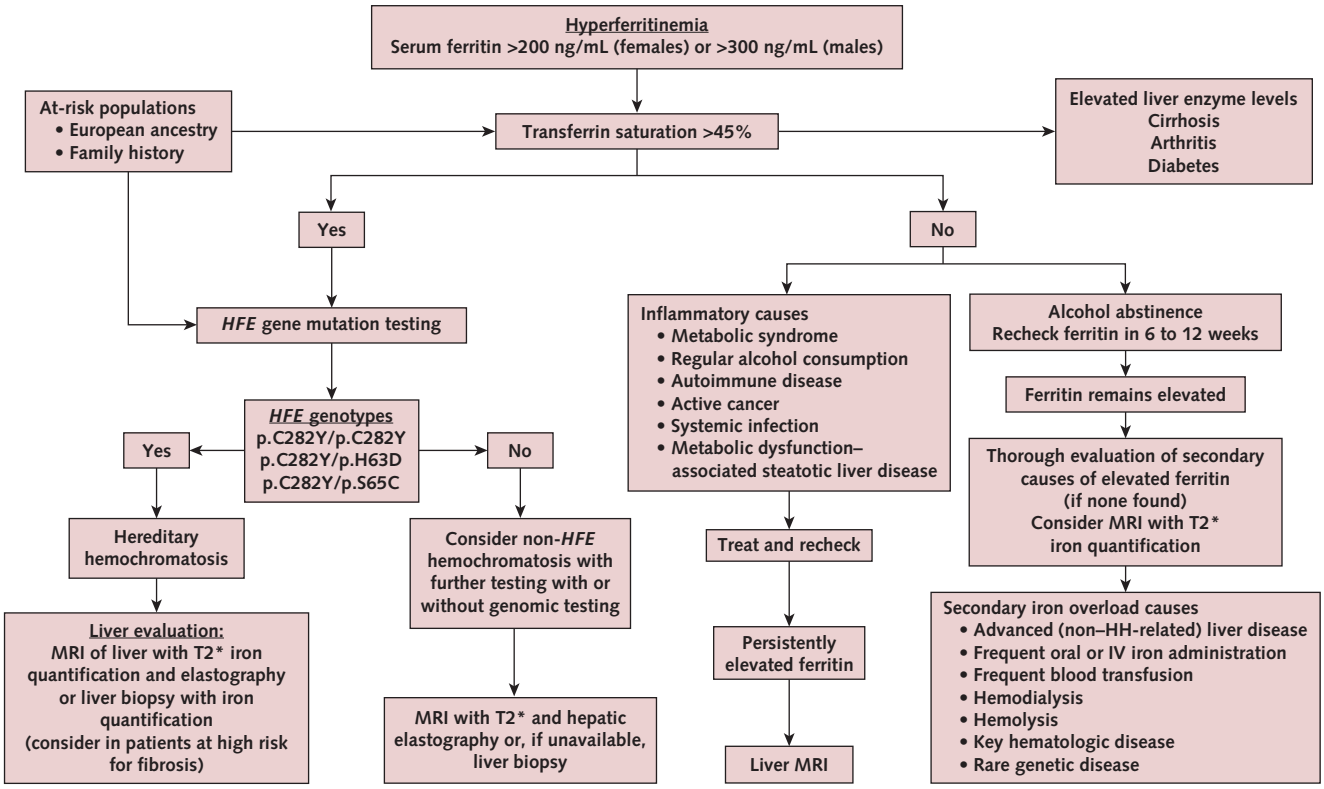
What should initial laboratory tests for a patient with suspected hemochromatosis include?

Because most patients are asymptomatic, diagnostic evaluation is often triggered by the incidental finding of elevated liver enzyme or ferritin levels as part of screening in high-risk patients or, less commonly, by hemochromatosis-related signs and symptoms. Initial evaluation should include both a ferritin test (if not already done) and a transferrin saturation test. The **Figure** summarizes the recommended diagnostic algorithm for patients with an elevated ferritin level, a common clinical scenario. A serum transferrin saturation greater than 45% is highly sensitive for hemochromatosis and, when combined with an elevated serum ferritin level greater than 200 ng/mL in females or greater than 300 ng/mL in males, provides approximately 97% sensitivity for systemic iron overload (3).

What is the role of genetic testing in screening and diagnosis of hemochromatosis?

If both serum transferrin saturation and serum ferritin level are found to be elevated (whether as part of a diagnostic work-up or screening), genetic testing for *HFE* variants should be performed. *HFE* gene testing should also be considered in patients with first-degree family members with any known *HFE* variants, even if serum iron levels are normal (3). Importantly, because causal iron-related genetic variants are not always identified in a minority of

Figure. **Diagnostic algorithm for patients with elevated serum ferritin level.**



HH = hereditary hemochromatosis; IV = intravenous; MRI = magnetic resonance imaging.

patients with hemochromatosis and iron overload phenotypes, a confirmatory positive result on a hemochromatosis-related gene analysis is not required for the diagnosis, and treatment should not be withheld.

Genetic testing begins with evaluation for the 3 most common *HFE* gene variants (p.C282Y/C282Y, p.C282Y/H63D, and p.C282Y/S65C), performed with a single commercial test (**Figure**). The p.C282Y/C282Y genotype has a 1.2% to 29% penetrance of iron overload (9). As many as 1 in 6 persons from key geographic areas may be carriers of a single variant. Two other less common *HFE*-associated hemochromatosis genotypes are compound heterozygotes of p.C282Y/p.H63D and p.C282Y/p.S65C, with both genotypes having less than 5% penetrance of iron overload (3) and presenting with milder forms of systemic iron overload. Similarly, compound homozygote of p.H63D (p.H63D/H63D) rarely predisposes people to systemic iron overload. Carrier states (wt/p.C282Y, wt/p.H63D, and wt/p.S65C) are not typically associated with *HFE*-associated hemochromatosis, but some studies suggest that these genotypes may predispose people to other conditions (26–28).

If a permissive pair of *HFE* variants as just outlined is not identified in a patient with screening laboratory test results suggesting hemochromatosis, non-*HFE* genetic testing may be considered in select patients for variants of HJV, HAMP, TfR2 variants, and ferroportin (SLC40A1) (12, 13). In cases where this advanced genetic testing is not available or cost limitations exist, non-*HFE* hemochromatosis may be a presumptive diagnosis and the patient may be managed appropriately. These recognized non-*HFE* variants are the cause of most non–*HFE*-associated hemochromatosis cases, but other

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undiscovered variants are also implicated (10, 11); thus, genetic confirmation may not be possible in all cases.

What are secondary causes of systemic iron overload?

Serum iron levels may be elevated in the absence of primary hemochromatosis. Therefore, "early closure" on a diagnosis of hemochromatosis should be avoided and secondary causes of iron overload should be considered in the appropriate clinical setting (see the **Figure** and the **Box:** Secondary Causes of Iron Overload), especially in patients of non-European descent. Secondary causes of systemic iron overload include frequent red blood cell transfusions; surreptitious oral iron intake; repeated parenteral iron infusions; and certain hematologic diseases, including myelodysplastic syndromes, thalassemia, and sickle cell disease (**Box:** Secondary Causes of Iron Overload). Frequent transfusions can lead to iron deposits in organs, particularly the liver and heart (3). Although exogenous oral iron supplementation rarely causes clinically important overload, parenteral iron infusions commonly lead to laboratory and imaging findings suggestive of increased systemic iron, which may take months to resolve. African iron overload is a secondary iron disorder commonly observed in sub-Saharan Africa and primarily associated with oral consumption of homemade beer with high iron content and cooking in cast iron pots (29).

Secondary Causes of Iron Overload

Exogenous iron loading
- Blood transfusion
- Parenteral/intravenous iron administration
- Excess oral iron supplementation or intake
- Hemodialysis

Hematologic disorders
- Hemolytic anemia
- β-Thalassemia
- Sickle cell anemia
- Hereditary spherocytosis
- Aplastic anemia

Chronic liver disease
- Viral hepatitis
- Porphyria cutanea tarda
- Metabolic dysfunction–associated steatotic liver disease

Chronic inflammatory conditions
- Inflammatory arthritis
- Autoimmune disease

Cancer
- Hepatocellular carcinoma

Secondary Causes of Elevated Serum Ferritin Levels

Metabolic syndrome
- Obesity
- Type 2 diabetes mellitus
- Hyperlipidemia

Infection
- Acute viral or bacterial infection
- Chronic systemic infection

Liver disease
- Metabolic
- Viral
- Autoimmune

Autoimmune disease

Regular alcohol use

Renal failure

Cancer

Alcohol use disorder, MASLD, and viral hepatitis have been associated with iron overload (high serum iron levels, transferrin saturation, and serum ferritin levels), including increased iron accumulation in the liver (3) (see the **Box:** Secondary Causes of Elevated Serum Ferritin Levels).

What other conditions should clinicians consider when evaluating a patient with hyperferritinemia in the absence of iron overload?

Hyperferritinemia may also present without iron overload (30). Elevated serum ferritin level without iron overload, commonly known as secondary serum ferritin elevation, encompasses approximately 90% of hyperferritinemia. Chronic liver disease, acute or chronic autoimmune or inflammatory conditions, regular alcohol use, metabolic syndrome, and obesity are common causes of elevated serum ferritin level without overload (22), likely because ferritin is an acute-phase reactant. One study suggests that up to 40% of people with an elevated serum ferritin level have neither *HFE* variants nor secondary causes of iron overload and the

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laboratory abnormality may be linked to obesity (31). Seasonal viral infections, such as influenza or COVID-19, may cause profound but short-lived elevations in serum ferritin level. Therefore, an elevated serum ferritin level is nonspecific, and clinicians should avoid "anchoring" on the diagnosis of hemochromatosis (32).

Obtaining other inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein level, may help differentiate elevated ferritin level due to underlying inflammation from systemic iron overload. Soluble transferrin receptor (sTfR) can also be measured as another indicator of systemic iron status (21). In an otherwise stable patient, repeating a serum ferritin test 4 to 6 weeks later may allow time for acute inflammatory processes to subside. Due to the effect of alcohol on serum ferritin, it is advisable to recheck levels after 3 months of abstinence in patients reporting high regular alcohol consumption.

What role does imaging play in the diagnosis of hemochromatosis?

Imaging is often unnecessary to establish the diagnosis of hemochromatosis but is indicated to evaluate for iron deposition within organs, particularly the liver. Although ultrasonography of the liver (without elastography) may show abnormal parenchyma, it often does not identify the cause of liver involvement (including iron deposits) or the level of fibrosis. Thus, guidelines recommend that patients with hemochromatosis and suspected liver involvement undergo magnetic resonance imaging (MRI) or liver biopsy to quantify iron deposition. Liver MRI for iron quantification combined with hepatic elastography (a measure of liver stiffness that reflects fibrosis) should be considered in patients with elevated serum iron levels and permissive hemochromatosis gene variants (22). MRI also quantifies iron deposition in the liver, heart, bone marrow, and spleen with reasonable accuracy using readily available and validated sequencing technology (33–35). Although hepatic steatosis may limit estimation of liver iron concentration, this has largely been mitigated by novel and improved MRI measurement protocols. Ultrasound-based elastography is routinely used to stratify risk for advanced liver fibrosis, but its role in the evaluation of hemochromatosis is poorly defined. Ultrasound is also useful in screening for HCC in patients with advanced liver fibrosis related to hemochromatosis (3).

Due to the fatty nature of the pancreas, noninvasive iron quantification MRI sequences are not well established. Nevertheless, although data are limited, expert opinion suggests that excess pancreas iron quantification on imaging is strongly associated with hemochromatosis.

Pituitary iron deposition may be quantified using MRI. However, routine brain MRI is not indicated.

Echocardiographic imaging for cardiac strain can identify patients with clinically relevant myocardial iron deposition and should be considered in all patients diagnosed with hemochromatosis (22, 36, 37). Dual-energy computed tomography has been proposed to quantify organ iron concentration, but its use in hemochromatosis has been limited (38).

What is the role of liver biopsy in establishing a diagnosis of hemochromatosis?

Advances in imaging technology have reduced the need for liver biopsy in patients with iron overload. Liver biopsy is reserved for those with suspected underlying autoimmune disease or MASLD (as these clinical disorders may occur concomitantly with or mimic hemochromatosis) or to evaluate for liver fibrosis in patients with nonconfirmatory hepatic elastography (3), particularly when the initial serum ferritin level exceeds 1000 ng/mL due to the high risk for advanced liver fibrosis. Liver iron quantification via biopsy is particularly helpful in identifying secondary iron sequestration from MASLD, long-term alcohol use, and viral hepatitis, as these patients have a much lower liver iron concentration than those with hemochromatosis.

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When should clinicians consider referral to a specialist for diagnosis?

Primary care clinicians should feel empowered to order *HFE* genetic testing in the appropriate clinical scenario. Referral to subspecialists is typically reserved for scenarios where the diagnosis is unclear, a non-*HFE* variant is suspected, or a liver biopsy is indicated.

Diagnosis... The diagnosis of hemochromatosis is made via a thoughtful history and physical examination along with readily available serum laboratory tests. Serum ferritin level and serum transferrin saturation may be elevated in the absence of hemochromatosis; therefore, "early closure" on a diagnosis of hemochromatosis should be avoided and secondary causes of iron overload should be excluded. Genetic testing should be considered in patients with an elevated serum ferritin level and a transferrin saturation above 45%. Advanced imaging technologies are used to assess severity of organ involvement and limit the need for diagnostic liver biopsy. Referral to subspecialists should be considered when the diagnosis is uncertain, when non-*HFE* hemochromatosis is suspected, or in the setting of advanced organ dysfunction.

CLINICAL BOTTOM LINE

Treatment

What is the overall approach to management of patients with hemochromatosis?

Management of hemochromatosis is aimed at preventing complications and involves 3 key components: removal of initial iron overload, maintenance of target iron levels, and monitoring for potential complications (Table 2).

Patients with *HFE* genetic variants and evidence of iron overload (serum ferritin level >300 ng/mL [men] or >200 ng/mL [women]) should be treated with iron removal via phlebotomy or chelation to reduce and maintain serum ferritin levels at approximately 50 ng/mL indefinitely. This level is believed to reduce complications and improve symptoms and quality of life, based on expert opinion and guidelines (3). Complications of hemochromatosis, including hepatic, cardiac, and endocrine dysfunction, are typically managed in collaboration with subspecialist clinicians. Several population studies suggest a possible link to other types of cancer, including breast and colon cancer, in people harboring the *HFE* gene variant (26, 39); therefore, vigilance in routine screening protocols is important, although patients with *HFE* gene variants do not require earlier cancer screening compared with the general population.

Some patients may be found to have *HFE* genetic variants during recommended screening as a first-degree relative of a patient with hemochromatosis or during asymptomatic testing with commonly available direct-to-consumer genetic panel testing, yet they may not have evidence of systemic iron overload on laboratory tests or imaging. Although no specific guidelines exist for follow-up of these patients, some experts suggest rechecking serum ferritin levels every 1 to 2 years to monitor for development of systemic iron overload, particularly in women who are still menstruating. Surveillance recommendations for the non-*HFE* mutations are unclear.

What lifestyle and dietary changes are recommended for patients with hemochromatosis?

Dietary and lifestyle changes in hemochromatosis may limit further iron absorption and modestly reduce but not eliminate the need for phlebotomy (3). Thus, dietary consultation with a nutritionist may be considered. Dietary

39. Osborne NJ, Gurrin LC, Allen KJ, et al. HFE C282Y homozygotes are at increased risk of breast and colorectal cancer. Hepatology. 2010;51:1311-1318. [PMID: 20099304]

Table 2. **Treatment of Hemochromatosis Meeting Iron Overload Thresholds***

Treatment	*Dosing*	*Notes*
Phlebotomy (first-line)	Induction: Weekly to biweekly until target reached, as tolerated* Maintenance: Reduce to 3 to 4 treatments per year	Check hemoglobin/hematocrit level before each treatment; reduce frequency if hemoglobin level is <12 g/dL Prescription-driven blood donation can be implemented Evidence suggests reduction in liver and cardiac complications and improvement in quality of life if given early; arthritis, diabetes, hypogonadism unlikely to improve
Erythrocytapheresis (second-line)	Tailored to patient's sex, weight, total blood volume; lower frequency than phlebotomy	Expensive; produces less symptomatic anemia; may be beneficial in heart disease Limited evidence suggests no difference in short-term quality of life or adverse events compared with phlebotomy
Deferoxamine (chelating agent)	Subcutaneous or intravenous	Not approved by U.S. Food and Drug Administration for hemochromatosis; not recommended by some experts, but may be considered in patients with poor venous access or debilitating needle phobia Requires close monitoring for hearing loss and retinopathy; also renal and hepatic adverse effects

** Treatment is indicated for serum ferritin level ≥300 mg/dL in men and ≥200 mg/dL in women together with serum transferrin saturation ≥45%. Consensus is lacking on a definitive target, but most experts recommend <50 to 100 mg/dL.*

iron exists in 2 forms: inorganic (mostly ferric, the main component in Western diets) and organic heme from animals, and ferritin iron from animals and plants. The expressivity of *HFE* variant phenotypes is enhanced by alcohol and a diet rich in meat. One systematic review suggested that dietary restriction may reduce phlebotomy volumes by 0.5 to 1.5 L (40). Based on expert opinion, the ACG and EASL guidelines suggest that education and interventions to promote a healthier diet rich in fruits and vegetables and low in red meat may empower patients (2, 3). A vegetarian-lacto-ovo-poultry-pescetarian diet is an optimal alternative (41). Iron-enriched grains and supplements as well as vitamin C, which increases nonheme iron absorption, should be avoided. Ingestion of raw shellfish is advised against, particularly in patients with known cirrhosis, due to the risk for *Vibrio vulnificus* infection.

Patients with hemochromatosis should be counseled to abstain from consuming alcoholic beverages to limit the risk for increased iron absorption, hepatic inflammation, and cirrhosis as even moderate consumption increases iron deposition in the liver and brain (42).

What is the role of phlebotomy, and when should it be initiated?

Iron depletion is the main treatment of iron overload in hemochromatosis and is recommended by the ACG (3) and the EASL (2). Phlebotomy is the first-line treatment of hemochromatosis for patients with p.C282Y homozygosity and p.C282Y/H63D compound heterozygosity with evidence of iron overload, as it removes excess iron deposition and prevents complications related to chronic iron overload, including HCC (22). Phlebotomy is believed to reduce morbidity and mortality before cirrhosis develops. Retrospective longitudinal studies suggest that maintenance phlebotomy leads to significant reductions in hepatic complications (3, 43, 44) and cardiomyopathy as well as improvement in fatigue and quality of life. However, diabetes, hypogonadism, and arthritis are unlikely to improve with iron removal (3).

*A systematic review of clinical outcomes of iron reduction in hemochromatosis published in 2020 included 24 studies (*n *= 5994) conducted between 1972 and 2018 (45). The majority of the studies were from Western Europe (67%)*

40. Moretti D, van Doorn GM, Swinkels DW, et al. Relevance of dietary iron intake and bioavailability in the management of HFE hemochromatosis: a systematic review. Am J Clin Nutr. 2013;98:468-479. [PMID: 23803887]
41. Milman NT. Managing genetic hemochromatosis: an overview of dietary measures, which may reduce intestinal iron absorption in persons with iron overload. Gastroenterology Res. 2021;14:66-80. [PMID: 34007348]
42. Topiwala A, Wang C, Ebmeier KP, et al. Associations between moderate alcohol consumption, brain iron, and cognition in UK Biobank participants: observational and mendelian randomization analyses. PLoS Med. 2022;19:e1004039. [PMID: 35834561]
43. Niederau C, Fischer R, Pürschel A, et al. Long-term survival in patients with hereditary hemochromatosis. Gastroenterology. 1996;110:1107-1119. [PMID: 8613000]
44. Falize L, Guillygomarc'h A, Perrin M, et al. Reversibility of hepatic fibrosis in treated genetic hemochromatosis: a study of 36 cases. Hepatology. 2006;44:472-477. [PMID: 16871557]
45. Prabhu A, Cargill T, Roberts N, et al. Systematic review of the clinical outcomes of iron reduction in hereditary hemochromatosis. Hepatology. 2020;72:1469-1482. [PMID: 32500577]

and North America (21%), and phlebotomy was the treatment studied in most of them (75% [n = 5737]). Only 3 studies were randomized controlled trials, and 90% of the nonrandomized studies had high risk of bias. Patients who were adequately treated, as defined by normalization of ferritin levels with serial phlebotomy, had higher cumulative survival than those who were not (76% vs. 36% at 10 years).

Phlebotomy is recommended when serum ferritin levels exceed 300 ng/mL in men and 200 ng/mL in women, together with a transferrin saturation of 45% or higher (2, 3). During the induction period, weekly to biweekly phlebotomy is recommended to reach a serum ferritin level of approximately 50 µg/L. However, expert opinion varies, and target levels may range from less than 50 µg/L to 100 µg/L. Most experts recommend avoiding use of transferrin saturation under 45% as a benchmark target, as this could precipitate iatrogenic anemia (22).

Phlebotomy intervals during induction are largely based on patient tolerance and development of anemia. Hemoglobin or hematocrit levels should be checked before every phlebotomy to guide frequency of subsequent treatments. Expert opinion suggests reducing phlebotomy frequency if the hemoglobin level is below 12 g/dL and pausing phlebotomy if it is below 11 g/dL.

During the maintenance phase, the number of phlebotomies may be reduced to 3 or 4 per year (3, 46, 47). Although serum ferritin is the most commonly used marker, sTfR has also been proposed as a predictor of iron depletion (48). Blood donation can be used as a form of phlebotomy prescribed by a clinician. The American Red Cross accepts patients with hemochromatosis as blood donors as long as they meet other eligibility criteria.

Erythrocytapheresis

Erythrocytapheresis, an isovolumic procedure in which erythrocytes are removed and saline or colloids are infused, is believed to reduce risk for iron overload–related cirrhosis and liver cancer (3). It is usually preferred by patients over phlebotomy and is particularly beneficial in those with cardiac disease because of the lower risk for symptomatic anemia related to phlebotomy. Erythrocytapheresis is customized to the patient's sex, weight, and total blood volume, reducing the number of yearly procedures compared with phlebotomy (49). However, it is more expensive than phlebotomy and is limited by the need for specially trained personnel and equipment (6).

A 2017 Cochrane review of interventions for hemochromatosis included 3 trials (n = 146) that compared phlebotomy and erythrocytapheresis (50). Only 1 trial (n = 38) showed no mortality or serious adverse events at 8 months. There was no difference in the proportion of patients with adverse events (42.1% vs. 52.6%) or short-term health-related quality of life in the phlebotomy group versus the erythrocytapheresis group.

Chelating agents

Although iron-chelating agents are rarely used and are not approved by the U.S. Food and Drug Administration for treatment of hemochromatosis, they are an alternative treatment for patients with poor response to phlebotomy or contraindications for venesection (6). Deferoxamine (DFO), a chelator that is administered either subcutaneously or intravenously due to its poor oral absorption, has been used in a limited number of patients with hemochromatosis. Patients receiving DFO must be monitored for its well-known complications, mainly hearing loss and retinopathy. Deferasirox (DFX) is the most-studied iron chelator in patients with hemochromatosis in terms of efficacy and can be used orally. Although it is well suited to patients with poor venous access or needle phobia (51), DFX is costly and some experts advise against its use because of hepatic and renal adverse effects (6).

46. Adams P, Altes A, Brissot P, et al; Contributors and Hemochromatosis International Taskforce. Therapeutic recommendations in HFE hemochromatosis for p.Cys282Tyr (C282Y/C282Y) homozygous genotype. Hepatol Int. 2018;12:83-86. [PMID: 29589198]
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50. Buzzetti E, Kalafateli M, Thorburn D, et al. Interventions for hereditary haemochromatosis: an attempted network meta-analysis. Cochrane Database Syst Rev. 2017;3:CD011647. [PMID: 28273330]
51. Aydinok Y. Iron chelation therapy as a modality of management. Hematol Oncol Clin North Am. 2018;32:261-275. [PMID: 29458731]

Proton-pump inhibitors

Proton-pump inhibitors, which reduce iron absorption by increasing gastric pH, are not routinely recommended for iron overload treatment (3).

How should clinicians manage and monitor for future complications of hemochromatosis?

Complications of hemochromatosis can largely be avoided by early identification and prevention of iron overload. However, in patients who sustain substantial systemic iron overload for decades, organ injury may lead to increased morbidity and mortality (3). Patients with iron overload–related liver inflammation or early fibrosis, arthralgias, fatigue, early cardiomyopathy, and hyperpigmentation may see improvement after completion of induction phlebotomy, but more advanced endocrine, arthritic, cardiac, and cirrhotic complications are unlikely to improve with iron removal (2).

Liver disease

As discussed, serologic screening and management of all causes of chronic liver disease are indicated at the time of hemochromatosis diagnosis (22). Vaccination against hepatitis A, hepatitis B, and pneumonia should be updated in patients with liver disease. Staging of liver disease with liver elastography should occur at the time of diagnosis or immediately after induction phlebotomy. Ideally, MRI-based hepatic elastography would be performed after induction phlebotomy to limit risk for a nondiagnostic value confounded by dense hepatic iron deposition (37). However, continued monitoring of noncirrhotic-stage liver disease after induction or maintenance phlebotomy using routine imaging and/or laboratory testing is not recommended (22).

Liver disease progresses faster in the presence of cofactors, such as alcohol use disorder, viral hepatitis, and metabolic dysfunction–associated steatohepatitis. The risk for HCC is multiplied by a factor of 12 in patients with hemochromatosis compared with unaffected adult patients, with a 20- to 200-fold increase when cirrhosis is present (22). Patients with cirrhotic-stage liver disease but no evidence of decompensation should be monitored with laboratory testing and liver imaging every 6 months to screen for HCC and other complications. Patients with cirrhosis should be referred to a liver specialist and be evaluated for prophylactic β-blockers and endoscopic screening for esophageal varices.

Arthritis

Arthritis is found in approximately one fourth of patients with hemochromatosis and affects quality of life (52). Typically, arthritis affects the second and third metacarpophalangeal joints and may progress to other joints of the upper and lower limbs and ultimately the axial skeleton. The presence of arthritis predicts liver disease, and both tend to co-occur (52). Arthritis symptoms can be managed using the same strategies as in osteoarthritis, with a combination of nonsteroidal anti-inflammatory drugs, acetaminophen, and physical therapy. More advanced hemochromatosis arthritis can be treated with steroid injection or joint replacement, with outcomes similar to those in osteoarthritis (22). Population-based data from the National Inpatient Sample suggest an association between hemochromatosis and hip replacement (53) and spinal fusion surgery (54). Patients should be counseled that improvement in hemochromatosis-associated arthritis after phlebotomy varies, with some experiencing progression despite adequate phlebotomy.

Cardiac disease

Iron deposition in the myocardium may impair cardiac function by producing diastolic dysfunction, restrictive cardiomyopathy, and ventricular dilation (55). Atrial and ventricular tachyarrhythmias may also result due to intracardiac iron and/or an associated progressive decrease in ejection fraction. The atrioventricular node seems to be particularly susceptible to

52. Andersson L, Powell LW, Ramm LE, et al. Arthritis prediction of advanced hepatic fibrosis in HFE hemochromatosis. Mayo Clin Proc. 2022;97:1649-1655. [PMID: 35422339]
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impairment. Once heart failure develops, usual treatments to remove excess iron yield no benefit (55). We recommend obtaining a baseline electrocardiogram and echocardiogram in all patients with symptomatic hemochromatosis (22), but routine follow-up cardiac testing is not recommended in the absence of new symptoms or physical examination findings. If echocardiography detects excessive iron deposition and ventricular strain, cardiac MRI may be necessary (36). Myocardial biopsy is rarely needed.

Endocrinopathy

Expert opinion suggests that patients with hemochromatosis should be screened for endocrine complications at the time of diagnosis (22) but do not need ongoing screening in the absence of symptoms except when otherwise recommended as part of routine care (3). However, clinical suspicion of diabetes, hypothyroidism, or hypogonadism should trigger an appropriate laboratory work-up.

Management of diabetes (56) and other endocrinopathies associated with hemochromatosis is similar to that recommended for patients without iron overload; observational data suggest treatment outcomes for diabetes associated with hemochromatosis are similar to outcomes for classic type 2 diabetes (3). The most commonly affected hormones are gonadotropins, mainly the ones that control testosterone production (3). Growth hormone deficiency with anterior pituitary iron deposition has been cited in several studies (57).

When should patients be referred to subspecialists for management?

Management of patients with clinical manifestations typically requires multidisciplinary care. Therapeutic phlebotomy can be prescribed and managed by any clinician who is comfortable with monitoring of relevant laboratory values, but patients who do not tolerate it and/or have difficulties with venous access may need to be referred to a hemochromatosis expert. Patients with advanced liver disease should be referred to a gastroenterologist for management of potential complications. Similarly, the presence of significant cardiac arrhythmias or heart failure should prompt referral to a cardiologist. Patients with nondiabetic endocrine deficiency may be referred to an endocrinologist for treatment planning. Patients with diabetes that has been refractory to routine management may be considered for subspecialty referral. Patients with hepatic decompensation, cardiac failure, or liver cancer should be transferred to a center with availability for organ transplant.

Treatment... The main treatment of hemochromatosis is iron removal by phlebotomy, the frequency of which should be guided by serum ferritin levels. Erythrocytapheresis may be a better option for patients with cardiac disease who do not tolerate significant volume fluctuations, but it is more expensive and technically complicated. Iron chelation therapy with DFO or DFX is reserved mainly for patients who do not respond to phlebotomy. Reduction of dietary iron does not eliminate the need for phlebotomy but may reduce phlebotomy volumes. After initial staging, routine testing to monitor for new complications is not indicated in the absence of signs or symptoms.

CLINICAL BOTTOM LINE

56. Crawford AL, Laiteerapong N. Type 2 diabetes. Ann Intern Med. 2024;177:ITC81-ITC96. [PMID: 38857502]
57. McNeil LW, McKee LC, Lorber D, et al. The endocrine manifestations of hemochromatosis. Am J Med Sci. 1983;285:7-13. [PMID: 6342390]
58. Crawford DHG, Ramm GA, Bridle KR, et al. Clinical practice guidelines on hemochromatosis: Asian Pacific Association for the Study of the Liver. Hepatol Int. 2023;17:522-541. [PMID: 37067673]

Since 2019, three major professional organizations–ACG, EASL, and the Asian Pacific Association for the Study of the Liver–have issued comprehensive clinical practice guidelines (2, 3, 58). These guidelines are consistent in their recommendations for screening, diagnosis, treatment, and monitoring and are based on a combination of systematic review of the evidence and expert opinion where evidence is lacking.

In the Clinic

Tool Kit

Hemochromatosis

Patient Information

www.niddk.nih.gov/health-information/liver-disease/hemochromatosis
Information on hemochromatosis from the National Institute of Diabetes and Digestive and Kidney Diseases.

Information for Health Professionals

www.journal-of-hepatology.eu/article/S0168-8278(22)00211-2/fulltext
Clinical practice guidelines on hemochromatosis from the European Association for the Study of the Liver.

https://journals.lww.com/ajg/fulltext/2019/08000/acg_clinical_guideline__hereditary_hemochromatosis.11.aspx
Clinical guidelines on hereditary hemochromatosis from the American College of Gastroenterology.

https://link.springer.com/article/10.1007/s12072-023-10510-3
Clinical practice guidelines on hemochromatosis from the Asian Pacific Association for the Study of the Liver.

WHAT YOU SHOULD KNOW ABOUT HEMOCHROMATOSIS

What Is Hemochromatosis?

Hemochromatosis is an inheritable condition where too much iron builds up in your body due to a genetic defect. Although most patients have no symptoms, in some patients, because the body cannot get rid of iron, the excess iron is deposited in different organs, leading to organ damage, lower quality of life, and shorter life expectancy.

What Are the Risk Factors?

Hemochromatosis is caused by mutations in different genes that more commonly occur in White people of European descent, with some of the mutations more likely to lead to symptoms and poorer health effects than others. Risk factors that lead to worse outcomes include:

- Male sex
- Older age at presentation
- Alcohol consumption
- Type 2 diabetes mellitus
- Homozygous p.C282Y genetic variant

What Are the Symptoms?

Most people with hemochromatosis do not have any symptoms. However, those with more severe forms of the condition may have symptoms due to iron deposits in organs such as the liver, heart, pancreas, endocrine glands, and joints. This can lead to symptoms, including arthritis and joint pain; symptoms from diabetes or high blood glucose, such as increased urination, increased thirst, numbness and tingling, and vision changes; loss of libido and symptoms of low thyroid levels, such as weight gain and weakness; palpitations; shortness of breath; leg swelling; tiredness; lightheadedness; and, in advanced cases of liver damage, easy bruising, bleeding, jaundice, and swelling of the legs. Deposits in the skin can cause browning.

How Is It Diagnosed?

Your doctor may obtain blood tests of your iron levels based on your family history, symptoms, or other abnormal blood test results. Your doctor may also order a genetic test or other imaging tests, such as an MRI.

How Is It Treated?

For patients with iron levels above a certain threshold, phlebotomy (drawing about a pint of blood at a time) on a regular basis is the most common way to decrease body stores of iron to maintain levels within a target range. Patients with this condition should avoid drinking alcohol and should limit their intake of red meat, iron-enriched grains, and vitamin C supplements (which can increase iron absorption).

Questions for My Doctor

- How serious is my hemochromatosis?
- Should I change my diet?
- Should I undergo treatment?
- Am I at risk for cirrhosis or liver failure?
- Should I see a specialist?

For More Information

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National Institute of Diabetes and Digestive and Kidney Diseases
www.niddk.nih.gov/health-information/liver-disease/hemochromatosis

Patient Information