COLLEGE of AMERICAN PATHOLOGISTS

Hereditary Hemochromatosis

Version: 3.0
Date: August 30, 2022, Reviewed December 6, 2022, December 29, 2025

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SYNOPSIS AND RELEVANCE

While the term *hemochromatosis* was used previously to refer broadly to iron overload, it has more recently been applied specifically to a genetic disorder in which pathogenic mutations lead to a clinicopathologic condition featuring iron overload and elevated transferrin saturation.[1] Mutations in at least five genes can contribute to hemochromatosis, but most cases are encountered in individuals of European ancestry and result from homozygosity for the p.C282Y variant in *HFE*.[2] *HFE*-related hemochromatosis is a common autosomal recessive disorder of iron metabolism with low penetrance that, if left untreated, can lead to severe complications from iron overload, including hepatic failure, diabetes, and malignancy.[3] Other *HFE* genotypes (eg, compound heterozygosity for p.C282Y and p.H63D) have much lower penetrance and account for only rare cases of hemochromatosis.

Unexplained elevation in serum transferrin saturation that is greater than (>) 45%, especially if reproducible on repeat testing, is an indication for *HFE* genetic testing.[4] A family history of hereditary hemochromatosis is another indication for *HFE* genetic testing. Selection of appropriate criteria for *HFE* genetic testing and accurate interpretation of test results to inform treatment and management are important considerations to optimize use of this test.

OBJECTIVES

1. Facilitate accurate interpretation of tests for iron overload and, if indicated, follow up genetic testing.
2. Optimize genetic hemochromatosis test ordering practices.
3. Support interpretation of hemochromatosis gene mutation test results that inform appropriate management and treatment decisions.

BACKGROUND

Serum ferritin, iron, iron binding capacity, and transferrin saturation are common laboratory studies used to evaluate iron status. Transferrin saturation normally ranges between 15-30%. Approximately 2% of the adult US population have highly elevated transferrin saturation levels (> 45%), which are associated with higher risk for all-cause mortality.[4]

High transferrin saturation is most often associated with secondary causes such as chronic blood transfusions, hemolytic disease, poisoning, or chronic liver disease (eg, viral hepatitis, alcohol use, porphyria). Less often, elevated transferrin saturation is a sign of hereditary hemochromatosis, an autosomal recessive disorder of iron metabolism. This is one of the most common hereditary disorders, affecting about 1 in 200 individuals of northern European descent.

The most important pathogenic *HFE* variant is p.C282Y (c.845G>A), with homozygosity for this variant accounting for most cases of clinical hemochromatosis. While compound heterozygosity for p.C282Y and p.H63D (c.187C>G) may contribute to hemochromatosis, this is typically the case only in the presence of a pathogenic mutation of another hemochromatosis-related gene and/or the presence of another predisposing environmental factor (eg, HCV infection, alcohol use disorder, metabolic-associated fatty liver disease). While more than 20 other pathogenic variants in the *HFE* gene have been identified, the vast majority of clinical hemochromatosis cases are associated with homozygous p.C282Y, while most of the remaining are associated with compound heterozygosity for p.C282Y/p.H63D or rarely p.C282Y/p.S65C (c.193A>T). These genotypes (especially homozygous p.C282Y) may be associated with toxic injury to the liver and other organs that can be prevented by removing iron by regular therapeutic phlebotomies.[5,6] Other genotypes, such as heterozygous p.C282Y or homozygous p.H63D, are not associated with complications and do not require treatment despite elevated transferrin saturation levels.

Nevertheless, some patients with non-severe genotypes undergo unnecessary phlebotomy, apparently due to misunderstanding about the clinical significance of these genetic test results.[7] Most targeted *HFE* gene tests detect p.C282Y and p.H63D; some may include p.S65C. Therefore, *HFE* genotype testing can be misapplied if the ordering provider does not understand the scope, limitations and intended use of the test.

Other rare genetic causes of iron overload, including juvenile onset forms, are associated with pathogenic variants in the *HJV* gene, which cause what has historically been called hemochromatosis type 2A, and the *HAMP* gene, which cause what has historically been called hemochromatosis type 2B.[1,8] Genetic testing for these genes should typically be evaluated and ordered by a medical specialist. In some cases in which a genetic iron overloading condition is suspected without evidence of *HFE*-related disease, whole-exome sequencing may be used to identify other genetic causes.[8]

HFE gene testing is indicated for asymptomatic individuals with elevated transferrin saturation.[9,10] A repeat transferrin saturation test on a fasting specimen can be helpful for confirmation before genetic testing. The p.C282Y/p.C282Y genotype is found in 90% of individuals with transferrin saturation greater than or equal to (≥) 45%.[9] Nevertheless, universal screening for iron overload by transferrin saturation in asymptomatic patients without a family history of hereditary hemochromatosis is not recommended.[4] *HFE* gene testing is not indicated for other conditions, such as polycythemia, which may be mistaken as a condition associated with iron overload.

While serum ferritin is also elevated in patients with hemochromatosis, this is usually due to secondary causes such as inflammation or tissue injury and does not accurately reflect iron status, especially if transferrin saturation is not likewise elevated.[12] Furthermore, abnormal transferrin saturation levels typically appear sooner than elevated serum ferritin in patients with early, asymptomatic hemochromatosis. Therefore, *HFE* gene testing is indicated when transferrin saturation is elevated, even when serum ferritin is normal. Elevated transferrin saturation (≥ 45%) is preferred over hyperferritinemia as an indicator for genetic testing.[13,14]

INSIGHTS

1. *HFE* gene testing for p.C282Y is indicated for patients with unexplained elevated transferrin saturation (≥ 45%) levels and/or with clinical findings suggestive of iron overload, and also for first-degree relatives of people with homozygous p.C282Y hemochromatosis.
2. The value of testing for p.H63D is controversial, as the risk of severe iron overload is low in patients with compound heterozygosity for p.C282Y/p.H63D or homozygosity for p.H63D.[15]
3. *HFE* testing for hereditary hemochromatosis is generally not indicated for screening or in patients with normal iron studies unless there is a family history.
4. Hyperferritinemia alone without elevated transferrin saturation should not be used as an indication for *HFE* gene testing.[14]
5. *HFE* genetic testing should only be performed once unless there is some concern about reliability of prior test results.

INTERVENTIONS

1. Elevated Transferrin Saturation Results

   Consider adding comments that trigger when elevated transferrin saturation results are reported to alert providers about the differential diagnosis for a possible iron overloading state. A sample comment follows:

   Abnormal elevated transferrin saturation: this is typically secondary to various hepatic or hemolytic conditions. Testing for hereditary hemochromatosis by HFE gene testing should be considered in asymptomatic patients or those with family history who have not previously been tested.

2. *HFE* Genetic Testing Orders

   a. Consider developing a genetic registry of patients who have been tested for *HFE* gene variants. Use the registry to check all new *HFE* genetic testing orders for duplicates. If a duplicate is found, defer repeat testing, and notify the ordering provider of prior test results.
   For institutions that have electronic health record functionality to screen test orders, use the system to add once per lifetime frequency restrictions to germline hereditary testing.

   b. If *HFE* testing is referred to a reference laboratory, check to see whether the client services department has a process to identify and defer testing on repeat orders for genetic conditions.

   c. If technically feasible, include indications for *HFE* gene testing in the order entry system. For example: *"Indications for testing include either unexplained elevation in transferrin saturation (≥ 45%) or family history of hemochromatosis."*

   d. Develop soft or hard-stop criteria that require laboratory or specialist consultation if *HFE* gene testing is ordered without elevated transferrin saturation and/or family history.

   e. Consider checking or testing for elevated transferrin saturation as a prerequisite for processing *HFE* gene test orders. Contact the provider for more information (family history, other indication) to confirm that *HFE* gene testing was the intended order if the transferrin saturation is less than (<) 45%.

3. *HFE* Genetic Test Results
   a. Provide specific interpretive information that accompanies specific genotype results that describe significance of the results and possible management options such as the following examples:
      - For homozygous p.C282Y or compound p.C282Y/p.H63D, p.C282Y/p.S65C genotypes: "*Consistent with hereditary hemochromatosis. Consider referral for potential evaluation and management. Consider referral for genetic counseling of patient and family."*
      - For heterozygous p.C282Y, or heterozygous p.H63D results with no second pathogenic variant detected: *"This HFE genotype is typically not associated with complications from hemochromatosis, however, consider referral for genetic counseling of patient and family. Please note, this assay does not test for other rare pathogenic variants in the HFE gene."*
      - For wild type results: "*Negative for HFE gene variants. Please note, this assay does not test for other rare pathogenic variants in the HFE gene."*
   b. Collaborate with therapeutic phlebotomy services to develop protocols for reviewing genotype results for patients referred for treatment to confirm that the patient has an appropriate diagnosis for treatment.

QUESTIONS AND ANSWERS

QUESTION 1 OBJECTIVE

Interpret clinical significance of heterozygous *HFE* pathogenic variants.

QUESTION 1

A 45-year-old G2 P2 pre-menopausal healthy white woman with no family history of hemochromatosis was found to have an elevated transferrin saturation of 48% (serum iron = 180 µg/mL; total iron binding capacity = 380 ug/dL) during a routine health visit. Serum ferritin was 390 ng/mL, and the liver panel was normal. Repeat testing showed similar results. Based on these findings, hemochromatosis gene testing was ordered, and results demonstrated a heterozygous p.C282Y variant.

Based on these results, which one of the following actions is most indicated?

A. Referral for therapeutic phlebotomy
B. Imaging study to screen for hepatic malignancy
C. Genetic counseling/testing of patient's two teenage sons.
D. Repeat *HFE* testing for confirmation
E. No other actions recommended

The correct answer is E since heterozygous mutation generally does not require treatment, and children are too young to warrant consideration for testing.

A is incorrect since heterozygous C282Y mutations are rarely associated with iron overload complications despite patients having abnormal serum iron and iron saturation results.
B is incorrect since heterozygous C282Y mutations are rarely associated with iron overload complications despite patients having abnormal serum iron and iron saturation results. Evaluation for other causes of the abnormal iron study results, including hepatic and hematologic disorders, is recommended.
C is incorrect since children are too young to warrant consideration for informed consent or testing for HFE genotyping.[4]
D is incorrect since reliability of mutation analysis is excellent. Furthermore, confirmation has little if any value, since the clinical and therapeutic significance of heterozygous C282Y mutation is negligible.

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QUESTION 2 OBJECTIVE
Understand indications for ordering *HFE* gene testing.

A 44-year-old man of Chinese descent undergoes routine laboratory testing one year after completing ledipasvir-sofosbuvir treatment for hepatitis C. Routine follow up laboratory examinations include the following results:

Test	Result	Reference Range
Serum ferritin	422 ng/mL H (High)	20-325 ng/mL
Iron	100 µg/dL	50-150 µg/dL
Total iron binding capacity	380 µg/dL	50-425 µg/dL
Transferrin saturation	26%	16-30%
Alanine aminotransferase	49 U/L H	10-45 U/L
Aspartate aminotransferase	66 U/L H	10-45 U/L

The patient recently read a magazine article about the "silent disease" of hemochromatosis and was worried about his persistently high ferritin level, although values had come down since completing treatment, but not returned to normal. He asked his gastroenterologist to order a genetic test for diagnosis of this condition. Considering his history and laboratory results, which one of the patient's following conditions would support genetic testing?

A. Hyperferritinemia
B. Persistently elevated transaminase levels
C. Asian descent
D. Prognosis – Hemochromatosis increases risk of hepatic cancer with HCV infection
E. None of the above

E is correct since none of the other answers support genetic testing for hereditary hemochromatosis. See explanations for incorrect answers.

A is incorrect since the patient's hyperferritinemia (422 ng/mL) is not severe (> 1,000 ng/mL) and is a secondary indication for testing compared to transferrin saturation, which in this patient is within the normal reference range. Furthermore, the observed elevation in ferritin is most likely due to residual hepatic disease from hepatitis C infection.
B is incorrect since elevation of liver enzymes alone is non-specific for hereditary hemochromatosis and is more likely due to cirrhosis secondary to hepatitis C infection.
C is incorrect since the prevalence of hereditary hemochromatosis is substantially lower in people of Asian descent compared to patients of northern European descent.
D is incorrect. While a combination of hereditary hemochromatosis with hepatitis C infection increases the risk of severe liver injury, failure, and cancer, that is not an indication to test for *HFE* gene variants unless other findings such as elevated iron saturation or family history support testing.

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QUESTION 3 OBJECTIVE
Understand reasons for repeating *HFE* genetic testing.

You are notified by a reference laboratory that an order for *HFE* gene test was temporarily deferred because the patient (a 63-year-old white woman) underwent the same study 6 months ago due to increased transferrin saturation (72%) results. Genetic testing showed compound heterozygosity for p.C282Y/p.H63D. Upon contacting the ordering physician about the duplicate order, which of the following responses would justify repeating the test?

A. The ordering provider wanted to confirm results before starting lifelong therapeutic phlebotomy treatments.
B. *HFE* testing in this individual's son did not detect either the p.C282Y or p.H63D variant.

C. The patient's naturopath advised her to recheck the test since her "liver was healthy."
D. The ordering provider meant to repeat the test and add the p.H65C variant which would inform treatment and prognosis.
E. None of the above; there is no indication to repeat the test.

B is the correct answer. Lack of either *HFE* genetic variant in this individual's son raise sufficient concern about a potential testing error (analytical or clerical) in mother or son that rechecking results is indicated.

A is incorrect. *HFE* genetic testing is reliable. While answer A might be considered as marginally acceptable, answer B is a stronger indication for repeat testing.
C is incorrect since hereditary hemochromatosis is frequently asymptomatic, especially in women and younger men.
D is incorrect since the compound heterozygous genotype excludes the possibility of other variants such as p.H65C.
E is incorrect since B is the strongest indication for testing.

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