HFE Hemochromatosis Testing

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedure addressed by this guideline</th>
<th>Procedure code</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFE Targeted Mutation Analysis (common variants)</td>
<td>81256</td>
</tr>
<tr>
<td>HFE Sequence Analysis</td>
<td>81479</td>
</tr>
<tr>
<td>HFE Deletion/Duplication Analysis</td>
<td>81479</td>
</tr>
</tbody>
</table>

What is HFE hemochromatosis

Definition

HFE hemochromatosis is characterized by inappropriately high absorption of iron by the small intestinal mucosa.

There is a phenotypic spectrum of HFE hemochromatosis which includes:

- Clinical HFE hemochromatosis, where individuals manifest end-organ damage secondary to iron overload;
- Biochemical HFE hemochromatosis, where transferrin-iron saturation is increased and the only evidence of iron overload is increased serum ferritin concentration; and
- Non-expressing C282Y homozygotes, where individuals have neither clinical manifestations of HFE hemochromatosis nor iron overload.

Clinical HFE hemochromatosis leads to excess iron absorption and storage in the liver, heart, pancreas, and other organs. Individuals who are untreated may experience the following symptoms: abdominal pain, weakness, lethargy, weight loss, arthralgias, diabetes mellitus, and increased risk of cirrhosis when the serum ferritin is higher than 1,000 ng/mL. Other findings may include progressive increase in skin pigmentation, congestive heart failure, and/or arrhythmias, arthritis, and hypogonadism. Clinical HFE hemochromatosis is more common in men than women.

HFE hemochromatosis is caused by mutations in the HFE gene and is inherited in an autosomal recessive manner. About 1 in 200 to 1 in 400 non-Hispanic whites in North America are affected with HFE hemochromatosis.
Among individuals of northern European ancestry, the prevalence of individuals homozygous for HFE C282Y variant is 2:1,000 to 5:1,000. In non-Hispanic whites in North America, the prevalence of HFE C282Y homozygotes is 1:200 to 1:400. The disorder is less common among African Americans, Hispanics, and Asians.¹

HFE hemochromatosis can be effectively treated in most people. Phlebotomy therapy can alleviate almost all symptoms of iron overload if initiated before organ damage occurs.³

When HFE hemochromatosis is suspected, serum iron studies, including transferrin saturation (TS) or unsaturated iron-binding capacity, are the first step in establishing a diagnosis. HFE genetic testing is recommended if TS greater than or equal to 45%.⁴

Current guidelines support HFE genetic testing in people with: ² ⁴ ⁵

- Serologic evidence of iron overload, considered to be a transferrin saturation greater than or equal to 45% and elevated ferritin
- A known family history of hemochromatosis
- A known family mutation in the HFE gene in a first degree relative

Test information

- HFE Mutation Analysis
  - Common changes in the HFE gene associated with HFE hemochromatosis are C282Y, H63D, and S65C.¹
  - C282Y and H63D are the most common and account for 87% of hereditary hemochromatosis in European populations.¹ The next most common cause are individually rare mutations.⁶ Many labs do not test for S65C because it accounts for <1% of HFE hemochromatosis.¹ There is controversy over whether the H63D variant causes clinical disease². The combination of these mutations determines both the chances of symptoms occurring and their severity.

- HFE sequencing and deletion/duplication analysis is also available and may be necessary for individuals who do not have northern European ancestry.¹

Guidelines and evidence

  - “In a patient with suggestive symptoms, physical findings, or family history, a combination of transferrin saturation (TS) and ferritin should be obtained rather than relying on a single test. (1B) If either is abnormal (TS ≥45% or ferritin above the upper limit of normal), then HFE mutation analysis should be performed. (1B)”
• “The guideline developers recommend screening (iron studies and HFE mutation analysis) of first-degree relatives of patients with HFE-related HH to detect early disease and prevent complications”

Screening for Hereditary Hemochromatosis: A Clinical Practice Guideline from the American College of Physicians (2005):³

• “Physicians should discuss the risks, benefits, and limitations of genetic testing in patients with a positive family history of hereditary hemochromatosis or those with elevated serum ferritin level or transferrin saturation. Before genetic testing, individuals should be made aware of the benefits and risks of genetic testing. This should include discussing available treatment and its efficacy; costs involved; and social issues, such as impact of disease labeling, insurability and psychological well-being, and the possibility of as-yet-unknown genotypes associated with hereditary hemochromatosis.”

Criteria

HFE known familial mutation testing

• Clinical Consultation:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous genetic testing of the HFE gene, AND

• Presymptomatic/Asymptomatic Genetic Testing:
  o HFE mutation identified in 1st degree biological relative, OR

• Diagnostic Testing:
  o Serologic evidence of iron overload, defined as transferrin saturation greater than or equal to 45% and/or elevated ferritin, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

HFE targeted mutation testing

• Clinical Consultation:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous genetic testing of the HFE gene, AND
• Presymptomatic/Asymptomatic Genetic Testing:
  o Documented family history of first-degree relative with HFE hemochromatosis, OR
• Diagnostic Testing:
  o Serologic evidence of iron overload, defined as transferrin saturation greater than or equal to 45% and/or elevated ferritin, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

**HFE gene sequence analysis**

• Clinical Consultation:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing:
  o No previous sequencing of the HFE gene, and
  o Previous targeted HFE genetic testing performed and zero or one mutation identified, AND
• Diagnostic Testing:
  o Serologic evidence of iron overload, defined as transferrin saturation greater than or equal to 45% and/or elevated ferritin, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

**HFE deletion/duplication analysis**

• Clinical Consultation:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Genetic Testing:
  o No previous deletion/duplication analysis of the HFE gene, and
  o Previous HFE sequencing performed and zero or one mutation identified, AND
• Diagnostic Testing:
  o Serologic evidence of iron overload, defined as transferrin saturation greater than or equal to 45% and/or elevated ferritin, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.
References


