Hereditary 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>
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<tr>
<td>HFE Targeted Mutation Analysis (common variants)</td>
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What is hereditary hemochromatosis

Definition

Hereditary hemochromatosis (HH) is an autosomal recessive genetic disorder that leads to excess iron absorption and storage in the liver, heart, pancreas, and other organs.¹

- Symptoms of hemochromatosis may include:¹,²
  - Hepatomegaly, liver disease, jaundice, cirrhosis, liver cancer
  - Heart disease, arrhythmia, cardiomyopathy
  - Unexplained weakness, chronic fatigue, apathy
  - Arthritis, arthralgia
  - Increased skin pigmentation (bronze color)
  - Weight loss, hair loss
  - Hypothyroidism, hypopituitarism
  - Amenorrhea, early menopause
  - Loss of libido, impotence
  - Adult-onset diabetes

- HH is caused by mutations in the HFE gene.¹ About 1 in 200 to 1 in 300 people in the U.S. are affected with HH.²

- HH is most common in Caucasians, with up to 11% of the population being carriers. The disorder is less common in African Americans and Hispanics, with the carrier prevalence being 2.3% and 3% respectively. HH is very rare in Asians, with less than 1 in 1000 being carriers.¹
HH can be effectively treated in most people. Phlebotomy therapy can alleviate almost all symptoms of iron overload if initiated before organ damage occurs. When hemochromatosis is suspected, serum iron studies, including serum ferritin and transferrin saturation, are the first step in establishing a diagnosis. Genetic testing of the HFE gene may follow if serum iron studies suggest the presence of iron overload.

Current guidelines support HFE genetic testing in people with: Serologic evidence of iron overload, considered to be a transferrin saturation >45% and elevated ferritin A known family history of hemochromatosis A known familial mutation in the HFE gene in a first degree relative

Test information

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

Guidelines and evidence

The American Association for the Study of Liver Diseases (AASLD) Practice Guidelines (2011): 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):
"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:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing of the HFE gene, AND
- Presymptomatic/Asymptomatic Genetic Testing:
  - HFE mutation identified in 1st degree biological relative, OR
- Diagnostic Testing:
  - 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:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing of the HFE gene, AND
- Presymptomatic/Asymptomatic Genetic Testing:
  - Documented family history of first-degree relative with HFE-related HH, OR
- Diagnostic Testing:
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


