Genetic Testing for Hereditary Hemochromatosis

Description

Hereditary hemochromatosis (HH), a common genetic disorder of iron metabolism, can lead to inappropriate iron absorption, toxic accumulation of iron, and organ damage. Genetic testing is available to assess variants in the human hemochromatosis (HFE) gene, which is responsible for most clinically significant cases of HH.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for human hemochromatosis improves the net health outcome in individuals with abnormal iron indices or clinical signs of iron overload. This review does not encompass genetic testing for human hemochromatosis (HFE) for those who are asymptomatic with a first-degree relative with known hereditary hemochromatosis, or who are asymptomatic for general population screening.

POLICY STATEMENT

Genetic testing for human hemochromatosis (HFE) gene variants may be considered medically necessary in a patient with abnormal serum iron indices indicating iron overload (see Policy Guidelines section).

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POLICY GUIDELINES

Serum Iron Indices for Diagnosing Hereditary Hemochromatosis

Elevated fasting transferrin saturation (the ratio of serum iron to total iron-binding capacity) is the most sensitive initial phenotypic screening test. A minimum cutoff value of 45% will detect almost all affected C282Y homozygotes.

Serum ferritin reflects body iron stores and generally rises later in the progression of iron overload. In the absence of other causes of hyperferritinemia (alcohol abuse, metabolic syndrome, inflammatory states [eg, infection, cancer, active rheumatoid arthritis], acute and chronic hepatitis), serum ferritin is a good marker of the degree of iron overload.

The negative predictive value of a normal transferrin saturation and serum ferritin is 97%. In this situation, no further testing is recommended.

The 2011 practice guidelines from the American Association for the Study of Liver Diseases (AASLD) recommended human hemochromatosis (HFE) gene variant testing in patients with abnormal serum iron indices (ie, serum ferritin and transferrin saturation), even in the absence of symptoms.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Variant of uncertain significance</th>
<th>Change in DNA sequence with uncertain effects on disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

**Genetic Counseling**

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**BENEFIT APPLICATION**

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**FDA REGULATORY STATUS**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

**RATIONALE**

**Summary of Evidence**

For individuals who have abnormal iron indices or clinical signs of iron overload who receive genetic testing for HFE, the evidence includes retrospective and prospective observational studies. The relevant outcomes are test accuracy, test validity, and change in disease status. Studies have demonstrated that current genetic testing detects the large majority of HH disease, but that, among those with positive tests (HH homozygotes), penetrance for clinical disease is low. There is no direct evidence of the clinical utility of genetic testing, but, along with prior knowledge of the effectiveness of treatment for clinical iron overload, there is a strong chain of evidence that supports the definitive genetic diagnosis of persons with early signs of HH. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Association for the Study of Liver Diseases

Practice guidelines from the American Association for the Study of Liver Diseases (2011) made the following statements on genetic testing for hereditary hemochromatosis (see Table 2).

Table 1. Guidelines on Genetic Testing for Hereditary Hemochromatosis

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
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<tr>
<td>“[We] recommend that patients with abnormal iron studies should be evaluated as patients with hemochromatosis, even in the absence of symptoms.”</td>
<td>A</td>
</tr>
<tr>
<td>&quot;In a patient with suggestive symptoms, physical findings, or family history [of HH], a combination of 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.”</td>
<td>1B</td>
</tr>
</tbody>
</table>

HH: hereditary hemochromatosis; TS: transferrin saturation.

U.S. Preventive Services Task Force Recommendations

A literature review by the U.S. Preventive Services Task Force (2006) concluded that evidence was not sufficient to support population screening for hemochromatosis. The Task Force "decided not to review the evidence again or update its recommendations" for hemochromatosis screening.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES


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**POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 2012</td>
<td>New policy</td>
<td>Policy updated with literature review. No changes to policy statement.</td>
</tr>
<tr>
<td>June 2013</td>
<td>Replace policy</td>
<td>Policy updated with literature review through March 23, 2014; references 1-4, 20-21 added; references 16-17 updated. No change in policy statements.</td>
</tr>
<tr>
<td>June 2014</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 1, 2015. References 1, 6 and 23 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through March 6, 2018; the reference list was revised and reordered, 6 references were removed, reference 15 added. The policy is revised with updated genetics nomenclature. “Mutations” changed to “variants” in policy statements. Policy statements otherwise unchanged.</td>
</tr>
</tbody>
</table>

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