Medical Policy
Genetic Testing for Hereditary Hemochromatosis

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Policy Number: 908
BCBSA Reference Number: 2.04.80
NCD/LCD: N/A

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Genetic testing for human hemochromatosis (HFE) gene variants may be considered MEDICALLY NECESSARY in a patient with abnormal serum iron indices indicating iron overload.

Serum Iron Indices in the Diagnosis of 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.
Genetic testing for HFE gene variants may be considered MEDICALLY NECESSARY in individuals with a family history of hemochromatosis in a first-degree relative.

Genetic Testing Of an Individual with a Family History of Hereditary Hemochromatosis
The 2011 practice guidelines from AASLD recommended screening (iron studies [serum ferritin and transferrin saturation] and HFE variant analysis) of first-degree relatives of patients with HFE-related hereditary hemochromatosis to detect early disease and prevent complications. For children of an identified proband, HFE testing of the other parent is generally recommended because, if results are normal, the child is an obligate heterozygote and need not undergo further testing because there is no increased risk of iron overload.

If C282Y homozygosity or compound heterozygosity is found in adult relatives of a proband, and if serum ferritin levels are increased, then therapeutic phlebotomy can be initiated. If ferritin level is normal in these patients, then yearly follow-up with iron studies is indicated. When identified, individuals with C282Y heterozygotes and H63D heterozygotes can be reassured that they are not at risk for developing progressive or symptomatic iron overload. Some individuals with H63D homozygotes can develop mild iron overload.

Genetic testing for hereditary hemochromatosis in screening of the general population is considered INVESTIGATIONAL.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required. Yes indicates that prior authorization is required. No indicates that prior authorization is not required. N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Inpatient Service</th>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Commercial PPO and Indemnity</th>
<th>Medicare HMO BlueSM</th>
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CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Code Description</th>
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<tr>
<td>81256</td>
<td>HFE (hemochromatosis)(e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D)</td>
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ICD-9 Diagnosis Codes

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<th>ICD-9-CM diagnosis codes</th>
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<td>Disorders of iron metabolism code range</td>
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<td>Family history of other endocrine and metabolic diseases</td>
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ICD-10-CM Diagnosis Codes

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<tr>
<td>E83.110</td>
<td>Hereditary hemochromatosis</td>
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<td>E83.111</td>
<td>Hemochromatosis due to repeated red blood cell transfusions</td>
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<td>E83.118</td>
<td>Other hemochromatosis</td>
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<td>Hemochromatosis, unspecified</td>
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Description

IRON OVERLOAD SYNDROMES
Iron overload syndromes may be hereditary, secondary to another disease (eg, iron-loading anemias, parenteral iron overload, chronic liver disease, or dysmetabolic iron overload syndrome), or due to other miscellaneous conditions (eg, neonatal iron overload, aceruloplasminemia, congenital atransferrinemia).

Iron overload, if untreated, can lead to secondary tissue damage in a wide range of organs resulting in chronic liver disease (hepatic fibrosis, cirrhosis, hepatocellular carcinoma), endocrine dysfunction (diabetes, hypogonadism), arthralgia or arthritis (typically involving the second and third metacarpophalangeal joints), and cardiomyopathy (with either symptomatic cardiac failure or arrhythmias).

Hereditary hemochromatosis (HH), an autosomal recessive disorder, is the most commonly identified genetic disorder in white people, with an estimated prevalence of 1 in 250. However, fully expressed disease with end-organ manifestations is seen in less than 10% of affected individuals. Factors that influence phenotypic expression of human hemochromatosis (HFE; high iron-related HH [ie, the clinical appearance of iron overload]) are not clearly defined. Low clinical penetrance may be due to a complex interplay of genetic status and other factors such as age, sex, environmental influences, and comorbid diseases.

HH leads to inappropriate iron absorption from the intestine and progressive increase in intracellular iron concentrations. Untreated HH leads to premature death, usually by liver complications. Treatment to remove excess iron with serial phlebotomy is simple and effective, and if started before irreversible end organ damage, restores normal life expectancy.

Hereditary Hemochromatosis

Diagnosis
Patients with hemochromatosis may present with nonspecific systemic symptoms or specific organ related symptoms, or they may be asymptomatic. Clinical diagnosis of hemochromatosis is based on documentation of increased iron stores as demonstrated by abnormal serum iron indices, specifically elevated transferrin saturation and elevated serum ferritin concentration. Liver biopsy has been used to confirm diagnosis but is now generally limited to determining the degree of hepatic fibrosis and cirrhosis during disease management. Most patients with a diagnosis of hemochromatosis will exhibit a familial pattern, thereby confirming the diagnosis of HH. However, the familial pattern may not be obvious due to the large percentage of undiagnosed patients in some families, and further evaluation of family members may be required to establish whether a familial pattern is present.

General population screening for HH has been proposed because of the high prevalence of disease, absence of or nonspecific early clinical findings, specificity of findings once they appear, low cost of diagnosis and treatment, and high cost and low success rate of late diagnosis and treatment. However, because penetrance is low, and the natural history of asymptomatic individuals is unpredictable, support for population-based screening is lacking. A 2006 U.S. Preventive Services Task Force (USPSTF) review
of the literature suggested that 38% to 50% of individuals with C282Y homozygotes may develop iron overload, with 10% to 33% eventually developing hemochromatosis-associated morbidity. The American Academy of Family Physicians, Centers for Disease Control and Prevention, and USPSTF recommended against population-based general screening.

**Treatment**
The main treatment for patients with HH is periodic phlebotomy. While there has never been a randomized controlled trial comparing phlebotomy with no phlebotomy in the treatment of HH, there is evidence from nonrandomized studies that initiation of phlebotomy before the development of cirrhosis and/or diabetes will significantly reduce HH-associated morbidity and mortality.

**Genetics**
Most patients with HH have variants in the *HFE* gene, located on the short arm of chromosome. The *HFE* gene was identified and cloned in 1996. The most common variant in the *HFE* gene is C282Y, a missense variant that changes cysteine at position 282 in the HFE protein to tyrosine. Homozygosity for the C282Y variant is associated with 60% to 90% of all cases of HH. Additionally, 3% to 8% of affected individuals are heterozygous for this variant. Penetration for elevated serum iron indices among C282Y homozygotes is variable. However, penetration for characteristic clinical end points (ie, end-organ damage) is quite low. There is no test that can predict whether an individual with a C282Y homozygote will develop clinical symptoms. A specific variant in *PCSK7*, which is associated with iron metabolism, has been investigated as a possible predictor of cirrhosis risk in HH patients homozygous for the *HFE* C282Y variant.

Another significant *HFE* variant is referred to as H63D, which changes histidine at position 63 to aspartic acid. Homozygosity for H63D is insufficient to cause clinically significant iron overload in the absence of modifying factors. However, compound heterozygosity for C282Y/H63D has been associated with increased hepatic iron concentrations; approximately 1% to 2% of patients with this genotype will develop clinical evidence of iron overload, usually in the presence of another liver disease.

The clinical significance of a third *HFE* variant, S65C (serine at position 65 changed to cysteine), appears to be minimal. This rare variant displays very low penetrance. Compound heterozygosity for C282Y/S65C may confer a low risk for mild HH. Individuals who are heterozygous for S65C and either the wild-type (normal) or H63D alleles do not seem to be at an increased risk for HH. Other variants in *HFE* and in non-*HFE* genes (eg, transferrin receptor 2 [TFR2]) resulting in iron overload syndromes are rare.

With the advent of genetic testing in the late 1990s, *HFE*-related HH is now frequently identified in asymptomatic probands and in asymptomatic relatives of patients who are known to have the disease. Therefore, a genetic diagnosis can be made in subjects who have not yet developed phenotypic expression; these subjects have a genetic susceptibility to developing iron overload but may never do so. A 2000 consensus conference of the European Association for the Study of Liver Diseases led to recognition of different stages and progression of hemochromatosis. These stages were defined as:

1. Stage 1: Patients with "genetic susceptibility" who have the genetic disorder but no increase in iron stores.
2. Stage 2: Patients who have the genetic disorder and phenotypic evidence of iron overload but no tissue or end-organ damage.
3. Stage 3: Patients who have the genetic disorder with iron overload and iron deposition to the degree that tissue and end-organ damage occur.

**Summary**
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 are responsible for most clinically significant cases of hereditary hemochromatosis.
For individuals who have abnormal iron indices or clinical signs of iron overload who receive genetic testing for \textit{HFE}, the evidence includes retrospective and prospective observational studies. Relevant outcomes are test accuracy, test validity, and change in disease status. These studies have established high analytic validity of genetic testing. 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 on the effectiveness of treatment for clinical iron overload, there is a strong chain of evidence that supports 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.

For individuals who are asymptomatic with a first-degree relative with HH who receive genetic testing for \textit{HFE}, the evidence includes retrospective and prospective observational studies. Relevant outcomes are test accuracy, test validity, and change in disease status. These studies have established high analytic validity of genetic testing. 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 on the effectiveness of treatment for clinical iron overload, there is a strong chain of evidence that supports definitive genetic diagnosis of persons who are first-degree relatives of persons with HH. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic in the general population who are asymptomatic with no family history of hereditary hemochromatosis who receive genetic testing for \textit{HFE}, the evidence includes observational studies of screening in population samples. Relevant outcomes are test accuracy, test validity, and change in disease status. These studies have established population prevalence of genetic HH, and serve as partial evidence to estimate penetrance of disease. The low prevalence of HH homozygosity in the general population and incomplete penetrance of clinical disease do not support a chain of evidence for clinical utility of genetic testing in an unselected population. The evidence is insufficient to determine the effects of the technology on health outcomes.

\textbf{Policy History}

<table>
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<td>7/2017</td>
<td>BCBSA National medical policy review. “Mutations” changed to “variants” in policy statements. Policy statements otherwise unchanged. 7/2017</td>
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<td>11/2015</td>
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<tr>
<td>6/2015</td>
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<td>6/2014</td>
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<td>2/2013</td>
<td>New policy describing covered and non-covered indications.</td>
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\textbf{Information Pertaining to All Blue Cross Blue Shield Medical Policies}

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines
References


8. Vujic M. Molecular basis of HFE-hemochromatosis. Front Pharmacol. 2014;5:42. PMID 24653703


