Medical Coverage Policy

Genetic Testing: Hereditary Hemochromatosis

☐ Device/Equipment  ☐ Drug  ☐ Medical  ☐ Surgery  ☑ Test  ☐ Other

Effective Date: 12/18/2012  Policy Last Updated: 12/18/2012

☑ Prospective review is recommended/required. Please check the member agreement for preauthorization guidelines.

☑ Prospective review is not required.

Description:
Hereditary hemochromatosis (HH) is a genetic disorder that alters the body’s ability to regulate iron absorption. When correctly diagnosed, HH is easily and effectively treated, but if untreated, it can lead to severe organ damage. An estimated one million people in the United States have hereditary hemochromatosis with Caucasians of northern European descent at highest risk.

HH causes the body to absorb too much iron. Normally humans extract needed iron from food via the intestines. When there is an adequate amount of iron, the body reduces its absorption to avoid excessive accumulations. In a person with HH, the mechanism for regulating iron absorption is faulty and the body absorbs too much iron. Untreated HH leads to premature death, usually due to liver complications. Hemochromatosis is one of the few genetic diseases for which there is a relatively simple and effective therapy. The disease is treated by removing blood from the patient in order to lower the overall level of iron in the blood.

During the initial phase, the patient undergoes phlebotomy frequently to lower the level of iron. After the initial phase, phlebotomies are performed only as needed to keep iron levels normal. When phlebotomy is started early in the course of the illness, it can prevent most complications. But even if phlebotomy is begun after complications have occurred, the treatment can still decrease symptoms and improve life expectancy.

The HFE gene was first identified and cloned in 1996. The majority of patients with HH have mutations in the HFE gene, which is located on the short arm of chromosome 6. The most common mutation in the HFE gene is C282Y, a missense mutation that substitutes a cysteine residue for tyrosine at amino acid position 282 on the HFE protein. Homozygosity for the C282Y mutation is associated with 60-90% of all cases of HH. Additionally, 3-8% of individuals affected with HH are heterozygous for this mutation. Penetrance for elevated serum iron indices among C282Y homozygotes is relatively high, but not 100%. However, the penetrance for the characteristic clinical end points (end organ damage) is quite low. There is no test that can predict whether a C282Y homozygote will develop clinical symptoms.

The other significant mutation is referred to as H63D which results in the substitution of aspartic acid for histidine at position 63. Homozygosity for H63D is insufficient to cause clinically significant iron overload in the absence of modifying factors. However, heterozygosity for C282Y/H63D has been associated with increased hepatic iron concentrations; approximately 1-2% of patients with this genotype will develop clinical evidence of iron overload.

The clinical significance of a third HFE mutation, S65C, appears to be minimal. This rare variant displays very low penetrance. Compound heterozygosity for C282Y and 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.

With the advent of genetic testing in the late 1990s, HFE-related HH is now frequently identified in asymptomatic probands and in presymptomatic relatives of patients who are known to have the disease. (1) Therefore, a genetic diagnosis can be applied to individuals who have not yet developed phenotypic expression. These individuals have a genetic susceptibility to developing iron overload but may never do so. A consensus conference of the European Association for the Study of Liver Diseases in 2000 led to a recognition of the different stages and progression of hemochromatosis. These stages were defined as:

- **Stage 1**: those patients with the genetic disorder with no increase in iron stores who have “genetic susceptibility”.
- **Stage 2**: those patients with the genetic disorder who have phenotypic evidence of iron overload but who are without tissue or end organ damage.
- **Stage 3**: those individuals who have the genetic disorder with iron overload and have iron deposition to the degree that tissue and end organ damage occurs.

Testing for mutations in the HFE gene, which contributes to the majority of cases of hereditary hemochromatosis, can confirm a genetic etiology. If clinically indicated, serial phlebotomy may be initiated, leading to a restored normal life expectancy. Therefore, genetic testing for HFE gene mutations may be considered medically necessary for patients with a clinical suspicion of hemochromatosis (signs and symptoms of iron overload) or in patients with fasting serum iron indices that are suggestive of iron overload, as well as in individuals with a family history of hemochromatosis.

As hereditary hemochromatosis is common, general population screening has been proposed because of the high prevalence of the disease, the lack of early clinical or nonspecific early clinical findings, the simplicity and effectiveness of treatment, and the low success rate of late diagnosis and treatment. However, because the penetrance of the genotype is low, and the natural history of untreated individuals cannot be predicted, there is a lack of support for population-based screening. Therefore, genetic testing for hereditary hemochromatosis in screening of the general population is considered not medically necessary.

**Medical Criteria:**
Genetic testing for HFE gene mutations in individuals with an abnormal serum iron indices indicating iron overload (serum transferrin iron saturation greater than or equal to 45%) is **medically necessary**.

Genetic testing for hereditary hemochromatosis of the general population for individuals with family history or without signs and symptoms of disease is considered screening **and a contract exclusion**.

*A close blood relative typically refers to first degree (parent, full sibling, or offspring) and second degree (grandparent, grandchild, uncle, aunt, niece, nephew, or half-sibling) relatives*

**Policy:**
Genetic testing for hereditary hemochromatosis is considered medically necessary when the above listed medical criteria has been met. Prior authorization is required for BlueCHiP for Medicare and recommended for all other lines of business.

**Coverage:**
Benefits may vary between groups and contracts. Please refer to the appropriate Evidence of Coverage, Subscriber Agreement, or Benefit Booklet for applicable benefits/coverage.

**Coding:**

81256

*Also known as:*
Not applicable

Related topics:
Not applicable

Published:
Provider Update, February 2013

References:


Tavill AS. Diagnosis and Management of Hemochromatosis. AASLD Practice Guidelines;HEPATOLOGY;May 2001:1321-8.

History:
12/18/12  New policy approved.

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