The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is required.** Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

**Description**

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

**Background**

**Iron overload**

Iron overload syndromes may be hereditary, secondary to some other disease (e.g., iron-loading anemias, parenteral iron overload, chronic liver disease or dysmetabolic iron overload syndrome), or due to other miscellaneous conditions (e.g., neonatal iron overload, aceruloplasminemia, congenital atransferrinemia).

Iron overload, if left 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 metacarpo-phalangeal joints), and cardiomyopathy (either with symptomatic cardiac failure or arrhythmias).

Hereditary hemochromatosis (HH), an autosomal recessive disorder, is the most common, identified, genetic disorder in Caucasians and may be seen in approximately one in 250 Caucasians. However, fully expressed disease with end-organ manifestations is seen in less than 10% of those individuals. The factors that influence phenotypic expression of **HFE**-related HH (that is the clinical appearance of iron overload) are not clearly defined. The low clinical penetrance appears to be due to a complex interplay of genetic status and other factors such as age, sex, environmental influences and the presence of other 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 by removing excess iron with serial phlebotomy is simple and effective, and if started before irreversible end organ damage, restores normal life expectancy.

**Diagnosis of hemochromatosis**

Patients with hemochromatosis may present with nonspecific systemic symptoms, specific organ-related symptoms, or they may be asymptomatic. The 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 in the past to confirm diagnosis but is now generally limited to determining the degree of hepatic fibrosis and cirrhosis during management of the disease.
Genetic testing can confirm a hereditary nature of the iron overload.

**Genetics of hereditary hemochromatosis**

The majority of patients with HH have mutations in the *HFE* gene, which is on the short arm of chromosome 6. The *HFE* gene was identified and cloned in 1996. 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 endpoints (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:

1. Stage 1: those patients with the genetic disorder with no increase in iron stores who have “genetic susceptibility”.
2. Stage 2: those patients with the genetic disorder who have phenotypic evidence of iron overload but who are without tissue or end organ damage.
3. 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.

**Regulatory Status**

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

**Corporate Medical Guideline**

Genetic testing for *HFE* gene mutations may be considered **medically necessary** in a patient with abnormal serum iron indices indicating iron overload. (See Policy Guidelines)

Genetic testing for *HFE* gene mutations may be considered **medically necessary** in individuals with a family history of hemochromatosis in a first-degree relative. (See Policy Guidelines)
Genetic testing for hereditary hemochromatosis in screening of the general population is considered investigational.

Policy Guideline

**Serum iron indices in the diagnosis of HH**

Elevated fasting transferrin saturation (the ratio of serum iron to total iron-binding capacity) is the most sensitive initial phenotypic screening test. A cut-off 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 confounding causes of hyperferritinemia (alcohol abuse, the metabolic syndrome, inflammatory states and acute and chronic hepatitis), serum ferritin is a good marker of the degree of iron overload. (2)

The negative predictive value of a normal transferrin saturation and serum ferritin is 97%. In this situation, no further testing is recommended. (2)

2011 Practice Guidelines by the American Association for the Study of Liver Diseases recommend *HFE* gene mutation testing in patients with abnormal serum iron indices, even in the absence of symptoms (e.g., abnormal serum iron indices on routine screening chemistry panel).

**Genetic testing in an individual with a family history**

The 2011 Practice Guidelines by the American Association for the Study of Liver Diseases 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. (1) 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 loading.

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, C282Y heterozygotes and H63D heterozygotes can be reassured that they are not at risk for developing progressive or symptomatic iron overload. Occasional H63D homozygotes can develop mild iron overload.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. *Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.*

**References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.