2.04.80 Genetic Testing for Hereditary Hemochromatosis

<table>
<thead>
<tr>
<th>Original Policy Date:</th>
<th>Effective Date:</th>
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<tbody>
<tr>
<td>August 31, 2015</td>
<td>July 1, 2017</td>
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</table>

**Policy Statement**

Genetic testing for human hemochromatosis (HFE) gene variants may be considered **medically necessary** for either of the following conditions (see Policy Guidelines section):

- In a patient with abnormal serum iron indices indicating iron overload
- In individuals with a family history of hemochromatosis in a first-degree relative

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

**Policy Guidelines**

**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 [e.g., 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 (i.e., serum ferritin and transferrin saturation), even in the absence of symptoms.

**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.

**Genetics Nomenclature Update**

Human Genome Variation Society (HGVS) 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). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the Human Genome Organization (HUGO).
The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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></td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td>Familial variant</td>
<td></td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<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>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<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

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

There is a specific CPT code for genetic testing for HFE common variants:

- **81256**: HFE (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D)

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 are responsible for most clinically significant cases of hereditary hemochromatosis.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the
contract language will control. Please refer to the member’s contract benefits in effect at the
time of service to determine coverage or non-coverage of these services as it applies to an
individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from
denying Food and Drug Administration (FDA)-approved technologies as investigational. In these
instances, plans may have to consider the coverage eligibility of FDA-approved technologies on
the basis of medical necessity alone.

### Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory
service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the
Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be
licensed by CLIA 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

#### Background

Iron Overload Syndromes

Iron overload syndromes may be hereditary, secondary to another 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,
acero-plasminemia, 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),
diabetes 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 [i.e., 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 hereditary hemochromatosis may 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 6. 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. Penetrance for elevated serum iron indices among C282Y homozygotes is variable. However, penetrance for characteristic clinical end points (i.e., 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 (e.g., 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.

**Literature Review**

The most recent literature search was performed through March 23, 2017. This review addresses genetic testing categories 1a (diagnostic testing of an affected individual's germline to benefit the individual) and 3 (testing of an asymptomatic individual to determine future risk of disease) (see Appendix Table 1 for all genetic testing categories).

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease); and (3) clinical utility (i.e., how results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

A 2001 Technology Evaluation Center (TEC) Assessment on genetic testing for human hemochromatosis (HFE) gene variants related to hereditary hemochromatosis (HH) concluded the following:

- Genetic testing and counseling for HFE variants in the management of patients with symptoms of iron overload consistent with HH, in the setting of 2 consecutive transferrin saturation values of 45% or more and a serum ferritin value of less than 200-300 μg/L, met the TEC criteria.
- Genetic testing and counseling for HFE variants in asymptomatic relatives of subjects with HH also met the TEC criteria.

The Assessment did not address the use of genetic testing for HFE gene variants in screening of the general population.12

**Testing Individuals with Abnormal Iron Indices or Signs of Iron Overload**

**Clinical Context and Test Purpose**

The purpose of genetic testing of individuals with abnormal iron indices or clinical signs of iron overload is to determine the underlying cause of iron overload, detect disease at an earlier stage, and direct treatment to prevent irreversible organ damage.

The relevant question addressed in this evidence review is: Does genetic testing for HFE lead to improved health outcomes?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest includes individuals with abnormal iron indices or clinical signs of iron overload.

**Interventions**

The relevant intervention of interest is genetic testing for HFE.

**Comparators**

The relevant comparator of interest is standard clinical management without genetic testing.

**Outcomes**

The potential beneficial outcome of primary interest is early detection of disease to prevent disease complications of iron overload.
Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to unnecessary treatments (e.g., phlebotomy) that may not be efficacious. False-negative test results can lead to lack of appropriate treatments to prevent complications from iron overload.

**Timing**
The time frame for outcome measures varies from short-term development of clinical signs of iron overload to long-term complications such as liver failure and cirrhosis.

**Setting**
The primary setting would be in the primary care office where abnormal iron studies reveal iron overload.

**Analytic Validity**
Stuhmann et al (2005) initiated a pilot study on DNA-based screening of HH in Germany. A focus of the study was the analytic validity of different test methods. A total of 3961 subjects provided blood samples for testing of the C282Y HFE variant; of these, 3930 samples were successfully tested by 2 independent test methods (either polymerase chain reaction and restriction digest, reverse allele-specific oligonucleotide hybridization, solid-phase oligonucleotide ligation assay, or microarray [DNA-chip]). In all, 67 of the tested subjects were homozygous for C282Y; 42.6% of them already knew their HH clinical diagnosis prior to sending the blood sample. Iron accumulation with further signs or symptoms of HH was present in 8 (24%) of 34 newly diagnosed C282Y homozygous subjects. Of 7860 tests performed, 7841 (99.6%) gave correct results. The overall error rate was 0.24% (95% confidence interval [CI], 0.15% to 0.38%). The analytic specificity of the test methods for detecting homozygosity for C282Y was 100% (7726/7726 nonhomozygous test challenges; 95% CI, 99.95% to 100%), and the analytic sensitivity was 97% (130/134 homozygous test challenges; 95% CI, 92.5% to 99.2%). This evidence indicates that test methods for C282Y are robust and highly sensitive and specific.

**Clinical Validity**
Bryant et al (2008) conducted a systematic review of 15 electronic databases to April 2007 to evaluate the clinical validity and clinical utility of DNA testing in people suspected of having HH and in family members of those diagnosed with the disorder. Clinical validity, defined as the ability of the test to detect or predict the phenotype (disorder) of interest, involved establishing the probability that the test would be positive in people with clinical HH (sensitivity) and the probability that the test would be negative in people without the disease (specificity). Studies were included if they reported the use of DNA tests in whites of northern European origin with iron overload suggestive of HH compared with a control population, and reported or allowed for the calculation of sensitivity and specificity.

Eleven observational studies were identified that evaluated the clinical validity of genotyping for the C282Y variant in the diagnostic workup for HH. Criteria used to define hemochromatosis varied among studies. The clinical sensitivity of C282Y homozygosity ranged from 28.4% to 100% when considering studies that used strict criteria to classify HH, the clinical sensitivity ranged from 91.3% to 92.4%.

**Section Summary: Clinical Validity**
Observational studies have demonstrated that pathogenic variants in the HFE gene are responsible for most clinically significant cases of HH. Studies that used strict criteria to classify HH revealed that the clinical sensitivity of genetic testing for HFE common variants is high.

**Clinical Utility**
There are no studies reporting direct evidence of the clinical utility of genetic testing. Thus, the clinical utility of genetic testing for HH relies on whether a strong chain of evidence exists. The chain of evidence extrapolates clinical utility in the absence of direct clinical studies that demonstrate clinical utility and relies on the established analytic and clinical validity of a genetic
test. Potential clinical utility via the chain of evidence shows how a genetic test result potentially impacts the diagnostic workup, alters patient management, and may lead to improved health outcomes.

**Section Summary: Clinical Utility**

Most individuals with HH can be diagnosed without genetic testing, based on a clinical diagnosis of hemochromatosis that occurs in a familial pattern. Individuals with an established diagnosis of HH will not directly benefit from genetic testing if irreversible organ damage has already occurred. However, some patients with signs and/or symptoms of HH may not have a definitive diagnosis after standard clinical workup. In these cases, genetic testing can confirm the diagnosis of HH when a pathogenic variant is identified. Following confirmation of diagnosis, management changes (i.e., treatment with phlebotomy) are likely to occur. Furthermore, early treatment of HH may prevent irreversible organ damage due to iron overload. As a result, genetic testing to confirm the diagnosis of HH has clinical utility in individuals with signs and symptoms of HH, but in whom a definitive diagnosis cannot be made without genetic testing.

**Testing Asymptomatic First-Degree Relatives**

**Clinical Context and Test Purpose**

The purpose of genetic testing of first-degree relatives of individuals with HH is to determine the need surveillance for iron overload, detect disease at an early stage, and initiate early treatment before irreversible organ occurs.

The relevant question addressed in this evidence review is: Does genetic testing for HFE in asymptomatic first-degree relatives lead to improved health outcomes?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest includes first-degree relatives of individuals with HH.

**Interventions**

The relevant intervention of interest is genetic testing for HFE.

**Comparators**

The relevant comparator of interest is standard clinical management without genetic testing.

**Outcomes**

The potential beneficial outcomes of primary interest are to determine the need for surveillance of iron overload, to detect disease at an earlier stage, and to prevent irreversible organ damage.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to unnecessary surveillance for iron overload and treatments (e.g., phlebotomy) that may not be efficacious. False-negative test results can lead to lack of surveillance for iron overload and treatments to prevent disease progression and irreversible organ damage.

**Timing**

The time frame for outcome measures varies from short-term development of clinical signs of iron overload to long-term complications such as liver failure and cirrhosis.

**Setting**

The primary setting would be in the primary care office where at-risk individuals are evaluated for risk of developing iron overload due to family history of HH.
Analytic Validity
See the discussion of analytic validity in the Testing Individuals with Abnormal Iron Indices or Signs or Symptoms of Iron Overload section.

Clinical Validity
Bulaj et al (2000) studied the prevalence of disease-related conditions among relatives of probands with hemochromatosis. The results showed that if the proband had a hemochromatosis-related condition, male relatives were more likely to have morbidity than if the proband had no hemochromatosis-related condition. Homozygous relatives were found to have hemochromatosis-related conditions that had yet to be detected clinically. The summary of results is shown in Table 1.

Table 1. Prevalence of Hemochromatosis-Related Conditions among Relatives of Probands

<table>
<thead>
<tr>
<th>Condition</th>
<th>Men (n=113)</th>
<th>Women (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron overload</td>
<td>96 (85%)</td>
<td>69 (68%)</td>
</tr>
<tr>
<td>≥1 hemochromatosis-related condition</td>
<td>43 (38%)</td>
<td>10 (10%)</td>
</tr>
<tr>
<td>≥1 hemochromatosis-related condition</td>
<td>27 (52%)</td>
<td>7 (16%)</td>
</tr>
</tbody>
</table>

≥1 hemochromatosis-related condition: Cirrhosis, hepatic fibrosis, elevated aminotransferase values, or hemochromatotic arthropathy.

Clinical Utility
There are no studies that report direct evidence on the clinical utility of genetic testing. Thus, the clinical utility of genetic testing for HH relies on whether a strong chain of evidence exists. The chain of evidence extrapolates clinical utility in the absence of direct clinical studies that demonstrate clinical utility and relies on the established analytic and clinical validity of a genetic test. Potential clinical utility via the chain of evidence shows how a genetic test result potentially impacts the diagnostic workup, alters patient management, and may lead to improved health outcomes.

Section Summary: Clinical Utility
Individuals with a first-degree relative with HH are at risk for developing the disease themselves. When there is a known pathogenic variant in the family, genetic testing of family members can confirm the presence or absence of the variant with a high degree of certainty. Homozygous relatives of patients with hemochromatosis have conditions related to hemochromatosis that were not previously detected clinically. For asymptomatic patients who test negative, surveillance for iron overload is not indicated. For asymptomatic patients who test positive, surveillance is indicated and early initiation of treatment may potentially prevent organ damage due to iron accumulation.

Testing Asymptomatic Individuals (Population Screening)
Clinical Context and Test Purpose
The purpose of genetic testing of individuals in the general population is to screen individuals without increased risk for iron overload for HFE genetic variants that might lead to abnormal iron indices and/or signs and symptoms of iron overload.

The relevant question addressed in this evidence review is: Does genetic testing for HFE in asymptomatic patients in the general population lead to improved health outcomes?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest includes individuals without increased risk for iron overload.

Interventions
The relevant intervention of interest is genetic testing for HFE.
Comparators
The relevant comparator of interest is standard clinical management without genetic screening.

Outcomes
The potential beneficial outcomes of primary interest are early detection of the disease to prevent disease complications of iron overload.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to unnecessary surveillance for iron overload and treatments (e.g., phlebotomy) that may not be efficacious. False-negative test results can lead to lack of surveillance for iron overload and treatments to prevent disease progression and irreversible organ damage.

Timing
The time frame for outcome measures varies from short-term development of clinical signs of iron overload to long-term complications such as liver failure and cirrhosis.

Setting
The principal setting would be in the primary care office.

Analytic Validity
See the discussion of analytic validity in the Testing Individuals with Abnormal Iron Indices or Signs or Symptoms of Iron Overload section.

Clinical Validity
See the discussion of clinical validity in the Testing Individuals with Abnormal Iron Indices or Signs or Symptoms of Iron Overload section.

Clinical Utility
McLaren and Gordeuk (2009) conducted the Hemochromatosis and Iron Overload Screening (HEIRS) study to evaluate the prevalence, genetic and environmental determinants, and potential clinical, personal, and societal impact of hemochromatosis and iron overload in a multiethnic, primary care-based sample of 101,168 adults enrolled over a 2-year period at 4 centers in the United States and 1 in Canada. Initial screening included genotyping for the HFE C282Y and H63D alleles, measurement of serum ferritin, and calculation of transferrin saturation. The yield of HFE genotyping for identifying persons with C282Y homozygosity was low in racial/ethnic groups other than non-Hispanic whites. Overall frequency of homozygosity for the C282Y variant in non-Hispanic whites was 4.4 per 1000. There was marked heterogeneity of disease expression in C282Y homozygotes. The authors concluded that (1) future studies to discover modifier genes that affect phenotypic expression in C282Y hemochromatosis should help identify patients who are at greatest risk of developing iron overload and may benefit from continued monitoring of iron status, and (2) although genetic testing is well-accepted and associated with minimal risk of discrimination, generalized population screening in a primary care population as performed in the HEIRS study was not recommended. This study was not designed to evaluate the efficacy of general population genetic screening, but the results are consistent with minimal clinical utility of such screening.

Section Summary: Clinical Utility
Individuals who are not at increased risk for developing HH will not likely benefit from genetic testing for HFE. Direct evidence of the clinical utility of genetic testing in the general population is lacking. In contrast to first-degree relatives of individuals with hemochromatosis, where a homozygous genotype is relatively strongly associated with clinically undetected iron overload or disease-related conditions, a chain of evidence cannot be constructed to show potential clinical utility or improvements in health outcomes from screening individuals not at increased risk for HH. The HEIRS study revealed that the prevalence of C282Y homozygotes in non-Hispanic
whites was 4.4 per 1000, or 0.44% in an unselected population. Given low homozygous frequency in the population and the variable penetrance of disease, long-term follow-up (e.g., 5-10 years) is required to determine the true clinical sensitivity (expected to be <0.44% due to variable penetrance). Additionally, in the absence of long-term prospective studies and observational treatment data, the chain of evidence does not show that identification of HFE common variants in an unselected, normal-risk population leads to improved outcomes.

**Summary of Evidence**

For individuals who have abnormal iron indices or clinical signs of iron overload who receive genetic testing for the human hemochromatosis (HFE) gene, 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 hereditary hemochromatosis (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 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 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.

**Supplemental Information**

**Practice Guidelines and Position Statements**

**American Academy of Family Physicians**
In 2006, the American Academy of Family Physicians recommended against routine genetic screening for hereditary hemochromatosis (HH) in the asymptomatic general population (grade D recommendation: at least fair evidence that [screening] is ineffective or that harms outweigh benefits).17

**American Association for the Study of Liver Diseases**
In 2011 practice guidelines, the American Association for the Study of Liver Diseases made the following statements on genetic testing for HH (see Table 2).2
Table 2. Guidelines on Genetic Testing for Hereditary Hemochromatosis

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
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<tbody>
<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>“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>
<tr>
<td>“[We] recommend screening (iron studies and ( HFE ) mutation analysis) of first-degree relatives of patients with HH-related HH to detect early disease and prevent complications.”</td>
<td>1A</td>
</tr>
<tr>
<td>“Average risk population screening for HH is not recommended.”</td>
<td>1B</td>
</tr>
</tbody>
</table>

HH: hereditary hemochromatosis; TS: transferrin saturation.

Centers for Disease Control and Prevention
The Centers for Disease Control and Prevention (2010) does not currently recommend population screening for \( HFE \) variants.\(^{18}\)

U.S. Preventive Services Task Force Recommendations
In 2006, a literature review by the U.S. Preventive Services Task Force (USPSTF) concluded that evidence was not sufficient to support population screening for hemochromatosis.\(^{1}\) USPSTF decided not to review the evidence again or update its recommendations for hemochromatosis screening.\(^{19}\)

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in January 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

Appendix

Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.80

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td>X</td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
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<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
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<tr>
<td>2b. Prognostic</td>
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<tr>
<td>2c. Therapeutic</td>
<td></td>
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<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td>X</td>
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<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
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</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td></td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
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</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
</tr>
<tr>
<td>5d. In utero testing: familial variants</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>

References

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

**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):
- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
2.04.80  Genetic Testing for Hereditary Hemochromatosis

1. Introduction

Genetic testing for hereditary hemochromatosis (HH) is a diagnostic tool used to identify the presence of the disease. HH is a genetic disorder that leads to iron accumulation in the body, especially in the liver, heart, and endocrine organs. This accumulation can cause serious health issues if left untreated.

2. Indications

The indication for genetic testing for HH includes:

- Comorbidities
- Activity and functional limitations
- Family history if applicable
- Reason for procedure/test/device, when applicable
- Pertinent past procedural and surgical history
- Past and present diagnostic testing and results
- Prior conservative treatments, duration, and response
- Treatment plan (i.e., surgical intervention)

3. Comorbidities

- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results
- Other pertinent multidisciplinary notes/reports: (e.g., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management) when applicable

4. Post Service

- Results/reports of tests performed

5. Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tr>
<td>CPT®</td>
<td>81256</td>
<td>HFE (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D)</td>
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<td>HCPCS</td>
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<tr>
<td>ICD-10 Procedure</td>
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<tr>
<td>ICD-10 Diagnosis</td>
<td>All Diagnoses</td>
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</table>

6. Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/31/2015</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>04/01/2016</td>
<td>Policy revision without position change</td>
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</tr>
<tr>
<td>07/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

7. Definitions of Decision Determinations

**Medically Necessary**: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not...
investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.