



Louisiana

Genetic Testing for Hereditary Hemochromatosis

Policy # 00430

Original Effective Date: 10/15/2014

Current Effective Date: 10/17/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing for human hemochromatosis (*HFE*) gene variants in a patient with abnormal serum iron indices indicating iron overload to be **eligible for coverage**.

Based on review of available data, the Company may consider genetic testing for human hemochromatosis (*HFE*) gene variants in individuals with a family history of hemochromatosis in a first-degree relative to be **eligible for coverage**.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for hereditary hemochromatosis (HH) in screening of the general population to be **investigational**.*

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.

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The 2011 practice guidelines from the American Association for the Study of Liver Diseases (AASLD) recommended *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 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

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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in

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subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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.

Background/Overview

Iron Overload Syndromes

Iron overload syndromes may be hereditary, secondary to some other 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 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 metacarpophalangeal joints), and cardiomyopathy (with either symptomatic cardiac failure or arrhythmias).

Hereditary Hemochromatosis

Hereditary hemochromatosis, an autosomal recessive disorder, is the most common 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 *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.

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Louisiana

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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 U.S. Preventive Services Task Force (USPSTF) review of the literature suggested that up to 38% to 50% of C282Y homozygotes may develop iron overload, with up to 10% to 33% eventually developing hemochromatosis-associated morbidity. The American Academy of Family Physicians, Centers for Disease Control and Prevention, and USPSTF recommend against population-based general screening.

Treatment

Treatment to remove excess iron with serial phlebotomy is simple and effective, and if started before irreversible end-organ damage, restores normal life expectancy. 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 mutation that changes cysteine at position 282 in the HFE protein to tyrosine. Homozygosity for the C282Y mutation is associated with 60% to 90% of all cases of HH. Additionally, 3% to 8% of affected individuals are heterozygous for this mutation. Penetrance for elevated serum iron indices among C282Y homozygotes is relatively high, but not 100%. However, penetrance for characteristic clinical end points (ie, end-organ damage) is quite low. There is no test that can predict whether 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

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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.

HFE-related HH is now frequently identified in asymptomatic probands and in presymptomatic 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 occurs.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

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

Rationale/Source

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

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The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

The evidence review was informed by a TEC Assessment (2001) on genetic testing for *HFE* gene variants related to HH. The Assessment concluded the following:

“...genetic testing and counseling for *HFE* mutations in the management of patients with symptoms of iron overload consistent with hereditary hemochromatosis, in the setting of 2 consecutive transferrin saturation values of 45% or more and a serum ferritin value of less than 200-300 mcg/L, meets the TEC criteria.

Genetic testing and counseling for *HFE* mutations in asymptomatic relatives of subjects with hereditary hemochromatosis also meets the TEC criteria.”

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

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.

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Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to unnecessary treatments (eg, 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.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Bryant et al (2008) conducted a systematic review of 15 electronic databases to April 2007 to evaluate the clinical validity and 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: Clinically Valid

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.

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Louisiana

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Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No studies reporting direct evidence of the clinical utility of genetic testing were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The clinical utility of genetic testing for HH relies on whether a strong chain of evidence exists.

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 (ie, 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.

Section Summary: Clinically Useful

For individuals who have abnormal iron indices or clinical signs of iron overload 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 the clinical disease is low. While there is no direct evidence of the clinical utility of genetic testing, a strong chain of evidence can be constructed that supports the definitive genetic diagnosis of persons with early signs of HH.

TESTING ASYMPTOMATIC FIRST-DEGREE RELATIVES WITH HH

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.

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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 test being considered is genetic testing for *HFE*.

Comparators

The following practice is currently being used: 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 false-positive or false-negative test results. False-positive test results can lead to unnecessary surveillance for iron overload and treatments (eg, 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 the 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 where at-risk individuals are evaluated for risk of developing iron overload due to family history of HH.

Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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Policy # 00430

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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

Condition	Men (n=113)	Women (n=101)
Iron overload, n (%)	96 (85)	69 (68)
≥1 hemochromatosis-related condition ^a	43 (38)	10 (10)
	Men >40 Years Old (n=52)	Women >50 Years Old (n=43)
≥1 hemochromatosis-related condition ^a	27 (52)	7 (16)

^a Cirrhosis, hepatic fibrosis, elevated aminotransferase values, or hemochromatotic arthropathy.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No studies that report direct evidence on the clinical utility of genetic testing were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The clinical utility of genetic testing for HH relies on whether a strong chain of evidence exists.

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.

Section Summary: Clinically Useful

For individuals who are asymptomatic with a first-degree relative with HH, studies have demonstrated that current genetic testing detects the large majority of HH disease, but that, among those with positive tests

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(HH homozygotes), penetrance for clinical disease is low. While there is no direct evidence of the clinical utility of genetic testing, a strong chain of evidence can be constructed that supports the definitive genetic diagnosis of persons who are first-degree relatives of persons with HH.

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 with no markers for 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 markers for increased risk for iron overload.

Interventions

The test being considered is genetic testing for *HFE*.

Comparators

The following practice is currently being used: routine clinical management without genetic screening.

Outcomes

The potential beneficial outcome of primary interest is early detection of the disease to prevent disease complications of iron overload.

Potential harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to unnecessary surveillance for iron overload and treatments (eg, 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 the 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.

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Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

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 *HFE* genotyping yield for identifying persons with C282Y homozygosity was low in racial/ethnic groups other than non-Hispanic whites. The 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.

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Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about 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 (eg, 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.

Section Summary: Clinically Useful

For individuals who are asymptomatic with no family history of HH, 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 does not support the clinical utility of genetic testing in an unselected population.

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. 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.

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. 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 who are first-

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Louisiana

Genetic Testing for Hereditary Hemochromatosis

Policy # 00430

Original Effective Date: 10/15/2014

Current Effective Date: 10/17/2018

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 with no family history of HH 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 does not support the clinical utility of genetic testing in an unselected population. The evidence is insufficient to determine the effects of the technology on health outcomes.

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|-----------------------------|---|
| 10/02/2014 | Medical Policy Committee review |
| 10/15/2014 | Medical Policy Implementation Committee approval. New policy. |
| 10/08/2015 | Medical Policy Committee review |
| 10/21/2015 | Medical Policy Implementation Committee approval. No change to coverage. |
| 10/06/2016 | Medical Policy Committee review |
| 10/19/2016 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes |
| 10/05/2017 | Medical Policy Committee review |
| 10/18/2017 | Medical Policy Implementation Committee approval. No change to coverage. The word mutation was replaced with variant. |
| 10/04/2018 | Medical Policy Committee review |
| 10/17/2018 | Medical Policy Implementation Committee approval. Added policy guidelines |
| Next Scheduled Review Date: | 10/2019 |

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Code Type	Code
CPT	81256
HCPCS	No codes
ICD-10 Diagnosis	E83.10 E83.110-E83.119 E83.19 Z83.49

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 - 3. Reference to federal regulations.

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- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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