



Louisiana

Genetic Testing for Hereditary Hemochromatosis

Policy # 00430

Original Effective Date: 10/15/2014

Current Effective Date: 11/09/2020

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.

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Serum ferritin reflects body iron stores and generally rises later in the progression of iron overload. In the absence of other causes of hyperferritinemia (alcohol abuse, metabolic syndrome, inflammatory states [eg, infection, cancer, active rheumatoid arthritis], acute and chronic hepatitis), serum ferritin is a good marker of the degree of iron overload.

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

The 2011 practice guidelines from the American Association for the Study of Liver Diseases (AASLD) recommended human hemochromatosis (*HFE*) gene variant testing in patients with abnormal serum iron indices (ie, serum ferritin and transferrin saturation), even in the absence of symptoms.

Genetic Testing 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.

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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 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.

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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 another disease (eg, iron-loading anemias, parenteral iron overload, chronic liver disease, dysmetabolic iron overload syndrome), or due to other miscellaneous conditions (eg, neonatal iron overload, aceruloplasminemia, congenital atransferrinemia).

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

Hereditary Hemochromatosis

HH, an autosomal recessive disorder, is the most commonly identified genetic disorder in white people, with an estimated prevalence of 1 in 250. However, fully expressed disease with end-organ manifestations is seen in less than 10% of affected individuals. Factors that influence phenotypic expression of human hemochromatosis (*HFE*; high iron-related HH [ie, the clinical appearance of iron overload]) are not defined. Low clinical penetrance may be due to the 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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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 the diagnosis but is now generally limited to determining the degree of hepatic fibrosis and cirrhosis during disease management. Most patients diagnosed with hemochromatosis will exhibit a familial pattern. 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 the 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 (2006) 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 U.S. Preventive Services Task Force have recommended 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 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,

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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 endpoints (ie, end-organ damage) is quite low. There is no test that can predict whether an individual with a C282Y homozygote will develop clinical symptoms. A specific variant in *PCSK7*, which is associated with iron metabolism, has been investigated as a possible predictor of cirrhosis risk in HH patients homozygous for the *HFE* C282Y variant.

Another significant *HFE* variant is 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 non-*HFE* genes (eg, transferrin receptor 2 [*TFR2*] gene) resulting in iron overload syndromes are rare.

HFE-related HH is now frequently identified by genetic testing 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 the recognition of different stages and progression of hemochromatosis. These stages were defined as:

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

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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.

Rationale/Source

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 is responsible for most clinically significant cases of HH.

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-degree relatives of persons with HH. The evidence is

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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.

Supplemental Information

Practice Guidelines and Position Statements

American Association for the Study of Liver Diseases

In 2011, the practice guidelines from the American Association for the Study of Liver Diseases made the following statements on genetic testing for hereditary hemochromatosis (see Table 1).

Table 1. Guidelines on Genetic Testing for Hereditary Hemochromatosis

Recommendation	Grade
"We recommend that family members, particularly first-degree relatives, of patients diagnosed with HH should be screened for HH."	A
"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 \geq 45% or ferritin above the upper limit of normal), then HFE mutation analysis should be performed."	1B
"[We] 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."	1A
"Average risk population screening for HH is not recommended."	1B

HH: hereditary hemochromatosis; TS: transferrin saturation.

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American College of Gastroenterology

In 2019, practice guidelines from the American College of Gastroenterology made the following statement on genetic testing for hereditary hemochromatosis: "We recommend that family members, particularly first-degree relatives, of patients diagnosed with HH should be screened for HH (strong recommendation, moderate quality of evidence)".

U.S. Preventive Services Task Force Recommendations

A literature review by the U.S. Preventive Services Task Force (2006) concluded that evidence was not sufficient to support population screening for hemochromatosis. The Task Force "decided not to review the evidence again or update its recommendations" for hemochromatosis screening.

Medicare National Coverage

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

Ongoing and Unpublished Clinical Trials

A search of [ClinicalTrials.gov](https://clinicaltrials.gov) in March 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

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Policy History

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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
- 10/03/2019 Medical Policy Committee review
- 10/09/2019 Medical Policy Implementation Committee approval. No change to coverage.
- 10/01/2020 Medical Policy Committee review
- 10/07/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 10/2021

Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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. Food and Drug Administration (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);

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- 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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