Genetic Testing for Hereditary Hemochromatosis

Policy # 00430
Original Effective Date: 10/15/2014
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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 HFE gene mutations 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 HFE gene mutations 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.*

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), arthropathy or arthritis (typically involving the second and third metacarpophalangeal joints), and cardiomyopathy (with either symptomatic cardiac failure or arrhythmias).

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.

Hereditary hemochromatosis leads to inappropriate iron absorption from the intestine and progressive increase in intracellular iron concentrations. Untreated HH leads to premature death, usually by liver
Genetic Testing for Hereditary Hemochromatosis

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complications. Treatment by removing excess iron with serial phlebotomy is simple and effective, and if started before irreversible end-organ damage, restores normal life expectancy.

Diagnosis of Hemochromatosis
Patients with hemochromatosis may present with nonspecific systemic symptoms 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 of HH
The main treatment modality for patients with HH is periodic phlebotomy. While there has never been a randomized controlled trial of phlebotomy versus 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 of HH
Most patients with HH have mutations in the \textit{HFE} gene, located on the short arm of chromosome 6. The \textit{HFE} gene was identified and cloned in 1996. The most common mutation in the \textit{HFE} gene is C282Y, a missense mutation that changes cysteine at position 282 in the \textit{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 \textit{PCSK7}, which is associated with iron metabolism, has been investigated as a possible predictor of cirrhosis risk in HH patients homozygous for the \textit{HFE} C282Y mutation.
Another significant mutation 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 mutation, 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 mutations in HFE and in non-HFE genes (eg, 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 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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA 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**

This evidence review was created in 2012 and is based on a search of the MEDLINE database through January 20, 2016. This review addresses BCBSA 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).
The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a mutation that is present or in excluding a mutation 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 (ie, 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).

Technology Assessments
A 2001 TEC Assessment on genetic testing for HFE gene mutations related to HH 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 µg/L, met the TEC criteria.
- Genetic testing and counseling for HFE mutations in asymptomatic relatives of subjects with hereditary hemochromatosis also met the TEC criteria.

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

Analytic Validity
Stuhramann et al (2005) initiated a pilot study on DNA-based screening of hereditary hemochromatosis 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 mutation; 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 the homozygotes already knew their clinical diagnosis of HH before 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). 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 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) evaluated the clinical validity and clinical utility of DNA testing in people suspected of having hereditary hemochromatosis and in family members of those diagnosed with the disorder by conducting a systematic review of 15 electronic databases (including MEDLINE and the Cochrane library) up to April 2007. 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 the...
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calculation of sensitivity and specificity. Clinical utility studies were included if they reported the use of DNA tests in whites with iron overload suggestive of HH (or relatives of suspected cases) compared with any case-identification strategy not involving DNA, and reported patient-based outcomes (eg, morbidity or mortality).

Eleven observational studies that evaluated the clinical validity of genotyping for the C282Y mutation in the diagnostic workup for HH were identified. Criteria used to define hemochromatosis varied among studies. Clinical sensitivity of C282Y homozygosity ranged from 28.4% to 100%; when considering studies that used strict criteria to classify HH, clinical sensitivity ranged from 91.3% to 92.4%. No clinical utility studies were found. The authors concluded that DNA testing for HH in at-risk populations has clinical validity and may have clinical utility.

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 or not a strong chain of indirect evidence exists.

Diagnostic Testing of an Individual’s Germline to Benefit the Individual
Individuals with an established diagnosis of HH will not benefit from genetic testing. Most individuals with HH can be diagnosed without genetic testing, based on a clinical diagnosis of hemochromatosis that occurs in a familial pattern. 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 mutation 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.

Testing Asymptomatic Individuals to Determine Future Risk of Disease
Individuals with a close relative with HH are at risk to develop the disease themselves. When there is a known pathogenic mutation in the family, genetic testing of family members can confirm the presence or absence of the mutation with a high degree of certainty. For patients who test negative, surveillance for iron overload is not necessary. For patients who test positive, surveillance is necessary and early initiation of treatment, often when patients are asymptomatic, may prevent organ damage due to iron accumulation.

Population Screening for HH
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 mutation 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 who 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 is 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.

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.

Summary of Evidence
The evidence for genetic testing for HH in individuals who have abnormal iron indices, clinical signs of iron overload, or are first-degree relatives of persons with hereditary hemochromatosis includes studies of analytic validity and clinical validity. 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 regarding the effectiveness of treatment for clinical iron overload, there is a strong chain of indirect evidence that supports definitive genetic diagnosis of persons with early signs of HH and of first-degree relatives of persons with HH. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for genetic testing for HH in individuals in the general population includes, in addition to the above studies of analytic and clinical validity, observational studies of screening in population samples. Relevant outcomes are test accuracy, test validity, and change in disease status. These studies establish population prevalence of genetic HH, and serve as partial evidence to estimate penetrance of disease. Results of these studies provide information regarding the chain of indirect evidence that might support general population screening. Low prevalence of HH homozygosity and incomplete penetrance of clinical disease do not support a chain of evidence that would support general population screening. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
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7. Vuijic M. Molecular basis of HFE-hemochromatosis. Front Pharmacol. 2014;5:42. PMID 24653703


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10/02/2014 Medical Policy Committee review
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

Next Scheduled Review Date: 10/2017

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*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:

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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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
Genetic Testing for Hereditary Hemochromatosis

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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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