BlueCross BlueShield of Alabama

Name of Policy:
Genetic Testing for Hereditary Hemochromatosis

Policy #: 546
Category: Laboratory

Latest Review Date: May 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *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.*

Description of Procedure or Service:

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

Iron Overload Syndromes

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

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

Hereditary Hemochromatosis

HH, an autosomal recessive disorder, is the most 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 <10% of those individuals. Factors that influence phenotypic expression of *HFE* (high iron-related HH (that is the clinical appearance of iron overload) are not defined. The low clinical penetrance appears to be due to a complex interplay of genetic status and other factors such as age, sex, environmental influences and the presence of other diseases.

HH leads to inappropriate iron absorption from the intestine and progressive increase in intracellular iron concentrations. Untreated HH leads to premature death, usually by liver complications.

Diagnosis

Patients with hemochromatosis may present with nonspecific systemic symptoms, specific organ-related symptoms, or they may be asymptomatic. The clinical diagnosis of hemochromatosis is based on documentation of increased iron stores as demonstrated by abnormal serum iron indices, specifically elevated transferrin saturation and elevated serum ferritin concentration. Liver biopsy has been used in the past to confirm diagnosis but is now generally limited to determining the degree of hepatic fibrosis and cirrhosis during management of the disease. Most patients with a diagnosis of 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 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 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 U.S. Preventive Services Task Force 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 of phlebotomy versus no phlebotomy in the treatment of HH, there is evidence from non-randomized 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, which is 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 60-90% of all cases of HH. Additionally, 3-8% of individuals affected with HH are heterozygous for this variant. Penetrance for elevated serum iron indices among C282Y homozygotes is variable. However, the penetrance for the characteristic clinical endpoints (end organ damage) is quite low. There is no test that can predict whether a C282Y homozygote will develop clinical symptoms. 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.

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 consensus conference of the European Association for the Study of Liver Diseases in 2000 led to

a recognition of the different stages and progression of hemochromatosis. These stages were defined as:

1. Stage 1: 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 have iron deposition to the degree that tissue and end organ damage occurs.

Policy:

Genetic testing for hemochromatosis meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage when one or more of the following criteria are met:

- Patient has abnormal serum iron indices indicating iron overload; **OR**
- Individual with a family history of hemochromatosis in a first-degree relative (parent, full sibling, or offspring).

Genetic screening of the general population for hereditary hemochromatosis **does not meet** Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was updated through March 6, 2018.

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.

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 human hemochromatosis (*HFE*) gene variants related to hereditary hemochromatosis (HH).[12] The Assessment concluded the following:

- Genetic testing and counseling for *HFE* variants in the management of patients with symptoms of iron overload consistent with hereditary hemochromatosis, in the setting of two consecutive transferrin saturation values of 45% or more and a serum ferritin value of less than 200–300 mcg/L, met the TEC criteria.
- Genetic testing and counseling for *HFE* variants in asymptomatic relatives of individuals with hereditary hemochromatosis 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.

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 test being considered 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 early detection of disease to prevent disease complications if 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 such as 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 outcomes 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.

Clinical Validity
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) 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 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 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 between studies. Clinical sensitivity of C282Y homozygosity for HH 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%.

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

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, 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.

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
Clinical Context and Test Purpose
The purpose of genetic testing of first-degree relatives of individuals with hereditary hemochromatosis 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 hereditary hemochromatosis.

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 and early detect disease at an earlier stage and 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 such as 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 outcomes 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 hereditary hemochromatosis.

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).

In 2000, Bulaj et al studied the prevalence of disease-related conditions among relatives of probands (n=291) 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 have 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 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 (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 without increased risk for iron overload for *HFE* genetic variants that may potentially 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 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 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 routine clinical management without genetic testing.

Outcomes

The potential beneficial outcomes of primary interest are early detection of disease to prevent disease complications if 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 such as 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 outcomes 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.

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 in 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 multi-ethnic, primary care-based sample of 101,168 adults enrolled over a two-year period at four centers in the U.S. and one in Canada. Initial screening included genotyping for the *HFE* C282Y and H63D alleles, measurement of serum ferritin, and a calculated transferrin saturation. The yield of *HFE* genotyping in identifying persons with C282Y homozygosity was low in racial/ethnic groups other than non-Hispanic whites. The overall frequency homozygosity for the C282Y variant in non-Hispanic whites was 4.4 per 1,000. 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 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.

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 hereditary hemochromatosis 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 in a relative strongly associates 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 to screen 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 to 10 years) is required to determine the true clinical

sensitivity (expected to be lower than 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 a genetic screening 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 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. 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 evidence that supports definitive genetic diagnosis of persons with early signs of HH. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with a first-degree with hereditary hemochromatosis 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 regarding 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals 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.

Practice Guidelines and Position Statements

American Academy of Family Physicians

In 2006, the AAFP recommended against routine genetic screening for hereditary hemochromatosis in the asymptomatic general population. (Grade D recommendation: at least fair evidence that [the service] is ineffective or that harms outweigh benefits).

American Association for the Study of Liver Diseases

A 2011 practice guideline from AASLD made the following statements on genetic testing for hereditary hemochromatosis:

- "[We] recommend that patients with abnormal iron studies should be evaluated as patients with hemochromatosis, even in the absence of symptoms." **(A)**
- "In a patient with suggestive symptoms, physical findings, or family history of HH, a combination of transferrin saturation and ferritin should be obtained rather than relying on a single test, and if either is abnormal (transferrin saturation ≥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)**

U.S. Preventive Services Task Force

In 2006, a literature review by the U.S. Preventive Services Task Force concluded that evidence was not sufficient to support population screening for hemochromatosis. USPSTF has "decided not to review the evidence again or update its recommendations" for hemochromatosis screening.

Key Words:

Hereditary hemochromatosis, Hemochromatosis, HFE, iron overload

Approved by Governing Bodies:

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.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply.

FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

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

References:

1. Adams P, Brissot P, Powell LW. EASL International Consensus Conference on Haemochromatosis. J Hepatol. Sep 2000;33(3):485-504.
2. Adams PC, McLaren CE, Speechley M et al. HFE mutations in Caucasian participants of the Hemochromatosis and Iron Overload Screening study with serum ferritin level <1000 microg/L. Can J Gastroenterol 2013; 27(7):390-2.
3. Adams PC, Speechley M, Kertesz AE. Long-term survival analysis in hereditary hemochromatosis. Gastroenterology 1991; 101(2):368-72.
4. Alexander J, Kowdley KV. HFE-associated hereditary hemochromatosis. Genet Med 2009; 11(5):307-13.
5. American Academy of Family Physicians. Hemochromatosis. 2006. Available online at: www.aafp.org/online/en/home/clinical/exam/hemochromatosis.html.
6. Bacon BR, Adams PC, Kowdley KV et al. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology 2011; 54(1):328-43.
7. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Genetic Testing for HFE Gene Mutations Related to Hereditary Hemochromatosis. TEC Assessments 2001; Volume 16, Tab 22: 20-5.
8. Bryant J, Cooper K, Picot J et al. A systematic review of the clinical validity and clinical utility of DNA testing for hereditary haemochromatosis type 1 in at-risk populations. J Med Genet 2008; 45(8):513-8.
9. Bulaj ZJ, Ajioka RS, Phillips JD, et al. Disease-related conditions in relatives of patients with hemochromatosis. N Engl J Med. Nov 23 2000; 343(21):1529-1535.
10. Centers for Disease Control and Prevention. Hemochromatosis (iron storage disease). Training-Epi Prevalence. 2010. Available online at: www.cdc.gov/ncbddd/hemochromatosis/training/epidemiology/prevalence.html.
11. Clark P, Britton LJ, Powell LW. The diagnosis and management of hereditary haemochromatosis. Clin Biochem Rev 2010; 31(1):3-8.
12. Crownover BK, Covey CJ. Hereditary hemochromatosis. Am Fam Physician 2013; 87(3):183-90.
13. Ekanayake D, Roddick C, Powell LW. Recent advances in hemochromatosis: a 2015 update: A summary of proceedings of the 2014 conference held under the auspices of Hemochromatosis Australia. Hepatology international 2015.
14. Gan EK, Powell LW, Olynyk JK. Natural history and management of HFE-hemochromatosis. Semin Liver Dis 2011; 31(3):293-301.
15. Kanwar P, Kowdley KV. Metal storage disorders: Wilson disease and hemochromatosis. Med Clin North Am 2014; 98(1):87-102.

16. McLaren GD, Gordeuk VR. Hereditary hemochromatosis: insights from the Hemochromatosis and Iron Overload Screening (HEIRS) Study. Hematology Am Soc Hematol Educ Program 2009:195-206.
17. Niederau C, Fischer R, Purschel A et al. Long-term survival in patients with hereditary hemochromatosis. Gastroenterology 1996; 110(4):1107-19.
18. Picot J, Bryant J, Cooper K et al. Psychosocial aspects of DNA testing for hereditary hemochromatosis in at-risk individuals: a systematic review. Genet Test Mol Biomarkers 2009; 13(1):7-14.
19. Radio FC, Majore S, Binni F et al. TFR2-related hereditary hemochromatosis as a frequent cause of primary iron overload in patients from Central-Southern Italy. Blood Cells Mol Dis 2014; 52(2-3):83-7.
20. Sood R, Bakashi R, Hegade VS et al. Diagnosis and management of hereditary haemochromatosis. British Journal of General Practice 2013; 63(611):331-32.
21. Stickel F, Buch S, Zoller H, et al. Evaluation of genome-wide loci of iron metabolism in hereditary hemochromatosis identifies PCSK7 as a host risk factor of liver cirrhosis. Human molecular genetics 2014; 23(14):3883-3890.
22. Stuhrmann M, Strassburg C, Schmidtke J. Genotype-based screening for hereditary haemochromatosis. I: Technical performance, costs and clinical relevance of a German pilot study. Eur J Hum Genet 2005; 13(1):69-78.
23. U.S. Preventive Services Task Force (USPSTF). Screening for hemochromatosis, August 2006. Available online at www.uspreventiveservicestaskforce.org/uspstf/uspshemoch.htm. Accessed March 2014.
24. Vujic M. Molecular basis of HFE-hemochromatosis. Front Pharmacol 2014; 5:42.
25. Whitlock EP, Garlitz BA, Harris EL et al. Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2006; 145(3):209-23.

Policy History:

Medical Policy Group, April 2011 **(1)** Genetic testing for hereditary hemochromatosis criteria developed
Medical Policy Administration Committee, April 2011
Available for comment April 13 – May 30, 2011
Medical Policy Panel, April 2012
Medical Policy Group, April 2012 **(1):** Update to Key Points and References; no change to policy statement
Medical Policy Panel, April 2013
Medical Policy Group, April 2013 **(1):** Update to Key Points and References; no change to policy statement
Medical Policy Group, January 2014 **(1):** Creation of individual policy with all references related to hemochromatosis removed from medical policy #136; addition of coverage criteria for individuals with first degree relatives with hemochromatosis, removal of criteria point of biopsy proven diagnosis
Medical Policy Administration Committee, February 2014
Available for comment February 5 through March 21, 2014
Medical Policy Panel, April 2014

Medical Policy Group, April 2014 **(1):** Update to Description, Key Points and References; no change to policy statement
Medical Policy Panel, April 2015
Medical Policy Group, May 2015 **(3)**: 2015 Updates to Description, Key Points, & References; no change in policy statement
Medical Policy Panel, February 2016
Medical Policy Group, February 2016 **(3)**: 2016 Updates to Description, Key Points, & References; no change in policy statement.
Medical Policy Panel, May 2017
Medical Policy Group, May 2017 **(3):** 2017 Updates to Description, Key Points, & References. No change in policy statement; removed policy statements effective prior to January 1, 2014.
Medical Policy Panel, May 2018
Medical Policy Group, May 2018 (4): Updates to Key Points, Key Words, Coding, and References. Removed HCPCS code S3837 which was deleted 4/1/12 from previous coding. No change to policy statements.
