2.04.80	Genetic Testing for Hereditary Hemochromatosis		
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Section:	2.0 Medicine	**Page:**	Page 1 of 16

Policy Statement

I. Genetic testing for human hemochromatosis (HFE) gene variants may be considered **medically necessary** for **either** of the following conditions (see Policy Guidelines section):
   A. In an individual with abnormal serum iron indices indicating iron overload.
   B. In individuals with a family history of hemochromatosis in a first-degree relative.

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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 [e.g., infection, cancer, active rheumatoid arthritis], acute and chronic hepatitis), serum ferritin is a good marker of the degree of iron overload.

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

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

Genetic Testing of an Individual With a Family History of Hereditary Hemochromatosis

The 2011 practice guidelines from AASLD recommended screening (iron studies [serum ferritin and transferrin saturation] and *HFE* variant analysis) of first-degree relatives of patients with *HFE*-related hereditary hemochromatosis to detect early disease and prevent complications. For children of an identified proband, *HFE* testing of the other parent is generally recommended because, if results are normal, the child is an obligate heterozygote and need not undergo further testing because there is no increased risk of iron overload.

If C282Y homozygosity or compound heterozygosity is found in adult relatives of a proband, and if serum ferritin levels are increased, then therapeutic phlebotomy can be initiated. If ferritin level is normal in these patients, then yearly follow-up with iron studies is indicated. When identified, individuals with C282Y heterozygotes and H63D heterozygotes can be reassured that they are not at risk for developing progressive or symptomatic iron overload. Some individuals with H63D homozygotes can develop mild iron overload.

Genetics Nomenclature Update

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 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

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

Description

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

Related Policies

- N/A

Benefit Application

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

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

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In November 2017, the 23andMe® Personal Genome Service (PGS) Genetic Health Risk was granted a de novo classification by the FDA (class II with general and special controls, FDA product code: PTA). This is a direct-to-consumer test that has been evaluated by the FDA for accuracy, reliability, and consumer comprehension. This test reports whether an individual has variants associated with HH and a higher risk of developing iron overload. This report is based on a qualitative genetic test for the C282Y (rs1800562) and H63D (rs1799945) variants in the *HFE* gene.

Rationale

Background

Iron Overload Syndromes

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

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 the phenotypic expression of HH (human hemochromatosis [*HFE]* gene; high iron-related HH [i.e., 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.

Hereditary hemochromatosis leads to inappropriate iron absorption from the intestine and a 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 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.[1,] 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.[1,]

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.[2,3,4,]

Genetics

Most patients with HH have variants in the *HFE* gene, located on the short arm of chromosome 6. The *HFE* gene was identified and cloned in 1996. The most common variant in the *HFE* gene is C282Y, a missense variant that changes cysteine at position 282 in the HFE protein to tyrosine. Homozygosity for the C282Y variant is associated with 60% to 90% of all cases of HH. Additionally, 3% to 8% of affected individuals are heterozygous for this variant. Penetrance for elevated serum iron indices among C282Y homozygotes is variable. However, penetrance for characteristic clinical endpoints (i.e., end-organ damage) is quite low. There is no test that can predict whether an individual with a C282Y homozygote will develop clinical symptoms. A specific variant in *PCSK7*, which is associated with iron metabolism, has been investigated as a possible predictor of cirrhosis risk in HH patients homozygous for the *HFE* C282Y variant.[5,]

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.[6,]

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 (e.g., transferrin receptor 2 [*TFR2*] gene) resulting in iron overload syndromes are rare.[7,8,9,10,]

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.[2,] 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.[11,] 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.

Literature Review

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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 PICO was used to select literature to inform this review.

Populations

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

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 outcome of primary interest is early detection of disease to prevent disease complications of iron overload. 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.

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

Study Selection Criteria
For the evaluation of clinical validity of genetic testing for macular degeneration, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

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).

Review of Evidence
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.[12,] 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%.

Eckerström et al (2020) performed a cohort study of blood donors in Sweden with signs of iron overload to investigate the feasibility and utility of an iron overload screening program to identify persons with *HFE* C282Y mutations.[13,] Among 50,493 blood donors newly registered between 1998 and 2015, 2864 were recommended for *HFE* genotyping based on transferrin saturation >50% or elevated serum ferritin (>130 mcg/L for men or >100 mcg/L for women). *HFE* typing was performed for 840 donors and identified a prevalence of C282Y homozygosity of 0.23%. The sensitivity and specificity for identification of C282Y homozygotes varied across men and women based on cutoff values for transferrin saturation and s-ferritin (Table 1).

Table 1. Sensitivity and Specificity of Screening for C282Y Homozygotes Based on Abnormal Iron Indices

	Men (n=668)		Women (n=172)	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Transferrin saturation >50%	84	56	81	38
Transferrin saturation >55%	76	70	77	61
Transferrin saturation >60%	71	80	60	76
Serum ferritin >130 mcg/L in men or >100 mcg/L in women	93	36	64	59
Serum ferritin >350 mcg/L in men or >150 mcg/L in women	63	94	41	88

Hasan et al (2022) retrospectively studied the penetrance of the C282Y/H63D compound heterozygote genotype in developing clinically significant iron overload using electronic health records of patients in Canada.[14,] Data were collected for up to 10 years following the initial genotyping. Between 1996 and 2009, 247 individuals tested positive for C282Y/H63D compound heterozygosity. At the time of genotyping, 4% of all patients had features of iron overload-related disease on the background of documented iron overload. Over the 10 years of follow-up, the proportion of patients with iron overload-related disease on the background of documented iron overload increased from 4% to 5.3%. The total number of patients with documented iron overload increased from 8.1% to 10.1%, the proportion of patients with provisional iron overload increased from 16.2% to 23.1%, and the number of patients with no evidence of iron overload decreased from 75.7% to 66.8%.

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.

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, more effective therapy, or avoid unnecessary therapy or 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 (RCTs).

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), clinical penetrance 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 Hereditary Hemochromatosis

Clinical Context and Test Purpose

The purpose of genetic testing of first-degree relatives of individuals with HH is to determine the need for surveillance for iron overload, to detect disease at an early stage, and to initiate early treatment before irreversible organ damage 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 PICO was used to select literature to inform this review.

Populations

The relevant population of interest is 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. 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.

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 (e.g., phlebotomy) that may not be efficacious. False-negative test results can lead to a lack of surveillance for iron overload and treatments to prevent disease progression and irreversible organ damage.

Study Selection Criteria

For the evaluation of clinical validity of genetic testing for macular degeneration, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

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).

Review of Evidence

Bulaj et al (2000) studied the prevalence of disease-related conditions among relatives of probands with hemochromatosis.[15,] 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 2.

Table 2. 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, more effective therapy, or avoid unnecessary therapy, or 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 RCTs.

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 (HH homozygotes), clinical penetrance 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 PICO was used to select literature to inform this review.

Populations
The relevant population of interest is 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: standard 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. 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.

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 (e.g., phlebotomy) that may not be efficacious. False-negative test results can lead to a lack of surveillance for iron overload and treatments to prevent disease progression and irreversible organ damage.

Study Selection Criteria
For the evaluation of clinical validity of genetic testing for macular degeneration, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

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).

Review of Evidence
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, more effective therapy, or avoid unnecessary therapy or 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 RCTs.

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 U.S. and 1 in Canada.[16,] 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 the 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 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 who are not at an 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 the low homozygous frequency in the population and the variable penetrance of disease, long-term follow-up (e.g., 5-10 years) is required to determine the true clinical sensitivity (expected to be <0.44% due to variable penetrance). Additionally, in the absence of long-term prospective studies and observational treatment data, the chain of evidence does not show that identification of *HFE* common variants in an unselected, normal-risk population leads to improved outcomes.

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 clinical penetrance does not support the clinical utility of genetic testing in an unselected population.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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 (HH) (Table 3).[2,]

Table 3. 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 ≥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.

American College of Gastroenterology

In 2019, practice guidelines from the American College of Gastroenterology made the following statement on genetic testing for HH: "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)".[17,]

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.[1,]The Task Force "decided not to review the evidence again or update its recommendations" for hemochromatosis screening.[18,]

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 in March 2023 did not identify any ongoing or unpublished trials that would likely influence this review.

References

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Family history, if applicable
  - Reason for test
  - Past and present diagnostic testing and results, including iron indices
  - Prior conservative treatments, duration, and response

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81256	HFE (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D)
HCPCS	None	

Policy History

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

Effective Date	Action
08/31/2015	BCBSA Medical Policy adoption
04/01/2016	Policy revision without position change
07/01/2017	Policy revision without position change
09/01/2018	Policy revision without position change
08/01/2019	Policy revision without position change
07/01/2023	Policy reactivated. Previously archived from 7/1/2020 to 6/30/2023.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

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

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

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an

authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Genetic Testing for Hereditary Hemochromatosis 2.04.80** **Policy Statement:** I. Genetic testing for human hemochromatosis (HFE) gene variants may be considered **medically necessary** for **either** of the following conditions (see Policy Guidelines section): A. In an individual with abnormal serum iron indices indicating iron overload. B. In individuals with a family history of hemochromatosis in a first-degree relative. II. Genetic testing for hereditary hemochromatosis for screening of the general population is considered **investigational**.