

Medical Policy



Nonprofit corporations and independent licensees
of the Blue Cross and Blue Shield Association

Joint Medical Policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. When Centers for Medicare and Medicaid (CMS) coverage rules are not fully developed, this medical policy may be used by BCBSM or BCN Medicare Advantage plans 42 CFR § 422.101 (b)(6). Please reference the appropriate certificate or contract for benefit information. This policy may be updated and is therefore subject to change.

***Current Policy Effective Date: 11/1/26**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Hereditary Hemochromatosis

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.

Medical Policy Statement

Genetic testing for hereditary hemochromatosis is **established** when criteria are met.

Genetic testing for hereditary hemochromatosis for screening of the general population is **experimental/investigational**. There is insufficient evidence to determine that the technology results in an improvement in net health outcomes.

Inclusionary and Exclusionary Guidelines

Inclusions:

Testing for *HFE* variants may be performed in:

- Individuals with a fasting transferrin saturation (the ratio of serum iron to total iron-binding capacity) $\geq 45\%$; OR
- Individuals with a serum ferritin level above the upper limit of normal; OR
- Individuals with a first-degree relative* diagnosed with *HFE*-related hereditary hemochromatosis

*A first-degree relative is a biological parent, full-sibling or child (someone who shares 50% of the individual's genes).

Exclusions:

- Screening for non-*HFE* related hereditary hemochromatosis
 - Screening for *HFE* variants in the general population
-

CPT/HCPCS Level II Codes**Established codes:**

81256

Other codes (investigational, not medically necessary, etc.):

N/A

Notes:

- *Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.*
 - *Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.*
-

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, or 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 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 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 or 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. 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.

Hereditary hemochromatosis is the most prevalent autosomal recessive condition in adults of Northern European descent.¹ In the United States, it affects approximately 1 in 300 non-Hispanic White individuals, and it is even more common, up to 1 in 150, among those of Northwestern European ancestry. An estimated 80% to 90% of clinically manifest HH cases result from homozygosity for the C282Y mutation in the *HFE* gene. Individuals with this genetic profile, particularly men, typically experience progressive iron accumulation as they age.

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. 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.²

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 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.^{3,4,5}

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 end points (i.e., 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.⁶

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.⁷

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.^{8,9,10,11}

HFE-related HH is now frequently identified in asymptomatic probands and in asymptomatic relatives of patients who are known to have the disease.³ 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.¹² 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 end-organ damage.
- Stage 3: Patients who have the genetic disorder with iron overload and iron deposition to the degree that tissue and end-organ damage occurs.

Summary of Evidence

For individuals who have abnormal iron indices or clinical signs of iron overload who receive genetic testing for human hemochromatosis (*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 hereditary hemochromatosis (HH) disease, but that among those with positive tests (HH homozygotes), clinical penetrance 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 that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a first-degree relative with HH who receive genetic testing for *HFE*, the evidence includes retrospective and prospective observational studies. Relevant outcomes are test accuracy, test validity, and change in disease status. Studies have demonstrated that current genetic testing detects the large majority of HH disease, but that among those with positive tests (HH homozygotes), clinical penetrance 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 that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with no family history of HH who receive genetic testing for *HFE*, the evidence includes observational studies of screening in population samples. Relevant outcomes are test accuracy, test validity, and change in disease status. These studies have established the prevalence of genetic HH, and serve as partial evidence to estimate clinical penetrance. The low prevalence of HH homozygosity in the general population and incomplete clinical penetrance do not support the clinical utility of genetic testing in an unselected population. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to individuals and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms. The following is a summary of the key literature to date.

TESTING INDIVIDUALS WITH ABNORMAL IRON INDICES OR SIGNS OF IRON OVERLOAD

Review of Evidence

Bryant et al (2008) conducted a systematic review of 15 electronic databases to April 2007 to evaluate 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.¹³ 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 Caucasians 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 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%.

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.¹⁴ 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.¹⁵ 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: 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.

Chain of Evidence

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

Review of Evidence

Bulaj et al (2000) studied the prevalence of disease-related conditions among relatives of probands with hemochromatosis.¹⁶ 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.

Direct Evidence

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

Chain of Evidence

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)

Review of Evidence

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

Direct Evidence

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

McLaren and Gordeuk (2009) conducted the Hemochromatosis and Iron Overload Screening (HEIRS) study to evaluate the prevalence, genetic and environmental determinants, and potential clinical, personal, and societal impact of hemochromatosis and iron overload in a multiethnic, primary care-based sample of 101,168 adults enrolled over a 2-year period at 4 centers in the United States and 1 in Canada.¹⁷ 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).³

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 hereditary hemochromatosis: "We recommend that family members, particularly first-degree relatives, of patients diagnosed with HH should be screened for HH (strong recommendation, moderate quality of evidence)".¹⁸

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.² The task force "decided not to review the evidence again or update its recommendations" for hemochromatosis screening, and the recommendations are currently inactive.¹⁹

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Regulatory Status:

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. Food and Drug Administration 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.

Government Regulations

National:

There is no national coverage determination (NCD) on the topic of genetic testing for hereditary hemochromatosis.

Local:

Wisconsin Physicians Service Insurance Corporation

Local Coverage Article Billing and Coding: MolDX Molecular Diagnostic Tests (A57772)
Original Effective Date 11/01/2019; Revision Effective Date 04/01/2026

Group 1 Codes:

81250 – 81259

Wisconsin Physicians Service Insurance Corporation

Local Coverage Determination MolDX Molecular Diagnostic Tests (MDT) (L36807)
Original Effective Date 02/16/2017; Revision Effective Date 05/29/2025

General coverage guidance; no specific information on this testing.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicaid Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing and Counseling

References

1. Grosse SD, Gurrin LC, Bertalli NA, et al. Clinical penetrance in hereditary hemochromatosis: estimates of the cumulative incidence of severe liver disease among HFE C282Y homozygotes. *Genet Med*. Apr 2018; 20(4): 383-389. PMID 28771247
2. 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*. Aug 01 2006; 145(3): 209-23. PMID 16880463
3. 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. PMID 21452290
4. Adams PC, Speechley M, Kertesz AE. Long-term survival analysis in hereditary hemochromatosis. *Gastroenterology*. Aug 1991;101(2):368-372. PMID 2065912
5. Niederau C, Fischer R, Purschel A, et al. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology*. Apr 1996;110(4):1107-1119. PMID 8613000
6. 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. *Hum Mol Genet*. Jul 15 2014;23(14):3883-3890. PMID 24556216
7. Kanwar P, Kowdley KV. Metal storage disorders: Wilson disease and hemochromatosis. *Med Clin North Am*. Jan 2014;98(1):87-102. PMID 24266916
8. Sood R, Bakashi R, Hegade VS, et al. Diagnosis and management of hereditary haemochromatosis. *British Journal of General Practice*. June 1, 2013 2013;63(611):331-332. PMID 23735405
9. Vujic M. Molecular basis of HFE-hemochromatosis. *Front Pharmacol*. 2014;5:42. PMID 24653703

10. 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.* Feb-Mar 2014;52(2-3):83-87. PMID 24055163
11. 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. *Hepatol Int.* Mar 12 2015. PMID 25788196
12. Adams P, Brissot P, Powell LW. EASL International Consensus Conference on Haemochromatosis. *J Hepatol.* Sep 2000;33(3):485-504. PMID 11020008
13. 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.* Aug 2008; 45(8):513-8. PMID 18310265
14. Eckerstrom C, Frandberg S, Lyxe L, et al. Evaluation of a screening program for iron overload and HFE mutations in 50,493 blood donors. *Ann Hematol.* Oct 2020; 99(10): 2295-2301. PMID 3284432
15. Hasan SMM, Farrell J, Borgaonkar M. C282Y/H63D Compound Heterozygosity Is a Low Penetrance Genotype for Iron Overload-related Disease. *J Can Assoc Gastroenterol.* Oct 2022; 5(5): 240-247. PMID 36196271
16. 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. PMID 11087882
17. McLaren GD, Gordeuk VR. Hereditary hemochromatosis: insights from the Hemochromatosis and Iron Overload Screening (HEIRS) Study. *Hematology Am Soc Hematol sEduc Program.* 2009:195-206. PMID 20008199
18. Kowdley KV, Brown KE, Ahn J, et al. ACG Clinical Guideline: Hereditary Hemochromatosis. *Am J Gastroenterol.* Aug 2019; 114(8): 1202-1218. PMID 31335359
19. U.S. Preventive Services Task Force (USPSTF). Hemochromatosis: Screening (inactive). 2006; <https://www.uspreventiveservicestaskforce.org/BrowseRec/InactiveTopic/219> Accessed 6/4/26
20. Wisconsin Physicians Service Insurance Corporation. Local Coverage Article Billing and Coding: MoIDX: Molecular Diagnostic Tests (MDT) (A57772). Revision effective date 4/1/2026.
21. Wisconsin Physicians Service Insurance Corporation. Local Coverage Determination MoIDX: Molecular Diagnostic Tests (MDT) (L36807). Revision effective date 5/29/2025.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through June, 2026, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/08	5/19/08	7/1/08	Joint policy established
5/1/10	2/16/10	2/16/10	Routine maintenance
1/1/12	10/11/11	11/9/11	Routine maintenance, Code update CPT 81256 added and CPT 88299 deleted
5/1/12	2/21/12	2/21/12	HCPSC code update - S3837 deleted effective 3/31/12
7/1/13	4/16/13	4/22/13	Routine maintenance
11/1/14	8/21/14	8/25/14	Routine maintenance Policy reformatted to mirror BCBSA
1/1/16	10/13/15	10/27/15	Routine maintenance Policy criteria updated
1/1/17	10/11/16	10/11/16	Routine maintenance
9/1/17	6/20/17	6/20/17	Routine maintenance References and rationale updated Added local Medicare coverage information "Mutations" changed to "variants" throughout policy
9/1/18	6/19/18	6/19/18	Routine maintenance
9/1/19	6/18/19		Routine maintenance Inclusions/criteria clarified Pg 7: per TEC, "less than 200-300mcg/L" is incorrect, should be "greater than". Corrected.
9/1/20	6/16/20		Routine maintenance; reference 16 added; WPS LCD and article added.
9/1/21	6/15/21		Routine maintenance
11/1/21	8/17/21		Routine maintenance Ref 14 added
11/1/22	8/16/22		Routine maintenance (ls)
11/1/23	8/15/23		Routine maintenance (jf) Added ref 14 Vendor Managed: NA

11/1/24	8/20/24		Routine maintenance (jf) Vendor Managed: NA
11/1/25	8/19/25		Routine maintenance (jf) Vendor Managed: NA The safety and effectiveness of removed from MPS, added, “when criteria are met” Patients removed and replaced with individuals Description added and background separated, movement of policy language and formatting to assist with flow
11/1/26	8/18/26		Routine maintenance (jf/no) Vendor Managed: NA Add Ref: 1 Minor Edits: - Added New MPS to align with existing exclusion on policy “Genetic testing for hereditary hemochromatosis for screening of the general population is experimental/investigational. There is insufficient evidence to determine that the technology results in an improvement in net health outcomes.” - Policy changed to Mixed Formatting changes made: - Notes edited in code section - Administrative Guidelines removed from Blue Care Network Coverage page

Next Review Date: 3rd Qtr, 2027

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR HEREDITARY HEMOCHROMATOSIS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, policy guidelines apply
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.