

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEMOCHROMATOSIS
POLICY NUMBER	MP 2.312

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

[POLICY](#)
[RATIONALE](#)
[DISCLAIMER](#)
[POLICY HISTORY](#)

[PRODUCT VARIATIONS](#)
[DEFINITIONS](#)
[CODING INFORMATION](#)

[DESCRIPTION/BACKGROUND](#)
[BENEFIT VARIATIONS](#)
[REFERENCES](#)

I. POLICY

Genetic testing for hereditary hemochromatosis (*HFE*) gene variants may be considered **medically necessary** in an individual with abnormal serum iron indices indicating iron overload. (See policy guidelines).

Genetic testing for *HFE* gene variants may be considered **medically necessary** in individuals with a family history of hemochromatosis in a first-degree relative. (See policy guidelines).

Genetic testing for hereditary hemochromatosis for screening of the general population is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure for this indication.

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.

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEMOCHROMATOSIS
POLICY NUMBER	MP 2.312

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 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

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEMOCHROMATOSIS
POLICY NUMBER	MP 2.312

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.

II. PRODUCT VARIATIONS

[TOP](#)

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

III. DESCRIPTION/BACKGROUND

[TOP](#)

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.

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).

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEMOCHROMATOSIS
POLICY NUMBER	MP 2.312

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 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 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 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.

General population screening for HH has been proposed because of the high prevalence of disease, absence of or nonspecific early clinical findings, specificity of findings once they appear, low cost of diagnosis and treatment, and high cost and low success rate of late diagnosis and treatment. However, because penetrance is low, and the natural history of asymptomatic individuals is unpredictable, support for population-based screening is lacking. A U.S. Preventive Services Task Force (2006) review of the literature suggested that 38% to 50% of individuals with C282Y homozygotes may develop iron overload, with 10% to 33% eventually developing hemochromatosis-associated morbidity. The American Academy of Family Physicians, Centers for Disease Control and Prevention, and U.S. Preventive Services Task Force have recommended against population-based general screening.

Treatment

Treatment to remove excess iron with serial phlebotomy is simple and effective, and if started before irreversible end-organ damage, restores normal life expectancy. While there has never

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEMOCHROMATOSIS
POLICY NUMBER	MP 2.312

been a randomized controlled trial comparing phlebotomy with no phlebotomy in the treatment of HH, there is evidence from nonrandomized studies that initiation of phlebotomy before the development of cirrhosis and/or diabetes will significantly reduce HH-associated morbidity and mortality.

Genetics

Most patients with HH have variants in the *HFE* gene, located on the short arm of chromosome 6. The *HFE* gene was identified and cloned in 1996. The most common variant in the *HFE* gene is C282Y, a missense variant that changes cysteine at position 282 in the HFE protein to tyrosine. Homozygosity for the C282Y variant is associated with 60% to 90% of all cases of HH. Additionally, 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 an individual with a C282Y homozygote will develop clinical symptoms. A specific variant in *PCSK7*, which is associated with iron metabolism, has been investigated as a possible predictor of cirrhosis risk in HH patients homozygous for the *HFE* C282Y variant.

Another significant *HFE* variant is 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 2000 consensus conference of the European Association for the Study of Liver Diseases led to the recognition of different stages and progression of hemochromatosis. These stages were defined as:

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

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEMOCHROMATOSIS
POLICY NUMBER	MP 2.312

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 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.

IV. RATIONALE

[TOP](#)

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 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 of 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 on 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

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEMOCHROMATOSIS
POLICY NUMBER	MP 2.312

penetrance. 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

[TOP](#)

FIRST-DEGREE RELATIVE refers to a parent, sibling, or child.

VI. DISCLAIMER

[TOP](#)

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

[TOP](#)

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes							
81256							

ICD-10-CM Diagnosis Code	Description
E83.10	Disorder of iron metabolism, unspecified
E83.110	Hereditary hemochromatosis
E83.111	Hemochromatosis due to repeated red blood cell transfusions
E83.118	Other hemochromatosis
E83.119	Hemochromatosis, unspecified
E83.19	Other disorders of iron metabolism
R79.0	Abnormal level of blood mineral
Z83.49	Family history of other endocrine, nutritional and metabolic diseases

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEMOCHROMATOSIS
POLICY NUMBER	MP 2.312

VIII. REFERENCES

[TOP](#)

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MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR HEREDITARY HEMOCHROMATOSIS
POLICY NUMBER	MP 2.312

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IX. POLICY HISTORY

[TOP](#)

MP 2.312	02/21/2020 Consensus Review. No change to policy statement. Coding reviewed.
	06/04/2021 Consensus Review. No change to policy statement. References and policy guidelines updated, and coding reviewed.
	07/05/2022 Consensus Review. No change to policy statement. FEP language and Regulatory Status updated.
	06/09/2023 Consensus Review. No change to policy statement. Policy Guidelines, Background, Rationale and References updated.
	06/18/2024 Consensus Review. No change to policy statement. References updated.
	05/02/2025 Consensus Review. No change to policy statement. Background, Benefit Variation and Disclaimer updated.
	01/16/2026 Retirement Review.

[TOP](#)

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