FEP Medical Policy Manual

FEP 2.04.80 Genetic Testing for Hereditary Hemochromatosis

Effective Policy Date: October 1, 2020

Original Policy Date: September 2012

Related Policies:

None

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.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for human hemochromatosis improves the net health outcome in individuals with abnormal iron indices or clinical signs of iron overload. This review does not encompass genetic testing for human hemochromatosis (HFE) for those who are asymptomatic with a first-degree relative with known hereditary hemochromatosis, or who are asymptomatic for general population screening.

POLICY STATEMENT

Genetic testing for human hemochromatosis (*HFE*) gene variants may be considered **medically necessary** in a patient with abnormal serum iron indices indicating iron overload (see Policy Guidelines section).

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 [eg, 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 (ie, serum ferritin and transferrin saturation), even in the absence of symptoms.

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

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient"s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Some Plans may have contract or benefit exclusions for genetic testing.

FDA 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. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

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), penetrance for clinical disease 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 the definitive genetic diagnosis of persons with early signs of HH. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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 (see Table 2).[2,]

Table 2. Guidelines on Genetic Testing for Hereditary Hemochromatosis

Recommendation	Grade
"[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.

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.[16,]

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.

REFERENCES

1. 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
2. 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. Jul 2011; 54(1): 328-43. PMID 21452290
3. Adams PC, Speechley M, Kertesz AE. Long-term survival analysis in hereditary hemochromatosis. Gastroenterology. Aug 1991; 101(2): 368-72. PMID 2065912
4. Niederau C, Fischer R, Purschel A, et al. Long-term survival in patients with hereditary hemochromatosis. Gastroenterology. Apr 1996; 110(4): 1107-19. PMID 8613000
5. 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): 3883-90. PMID 24556216
6. Kanwar P, Kowdley KV. Metal storage disorders: Wilson disease and hemochromatosis. Med Clin North Am. Jan 2014; 98(1): 87-102. PMID 24266916

7. Sood R, Bakashi R, Hegade VS, et al. Diagnosis and management of hereditary haemochromatosis. Br J Gen Pract. Jun 2013; 63(611): 331-2. PMID 23735405
8. Vujic M. Molecular basis of HFE-hemochromatosis. Front Pharmacol. 2014; 5: 42. PMID 24653703
9. 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): 83-7. PMID 24055163
10. 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. Apr 2015; 9(2): 174-82. PMID 25788196
11. Adams P, Brissot P, Powell LW. EASL International Consensus Conference on Haemochromatosis. J Hepatol. Sep 2000; 33(3): 485-504. PMID 11020008
12. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Genetic testing for HFE gene mutations related to hereditary hemochromatosis. TEC Assessments. Dec 6 2001;Volume 16:Tab 22. PMID
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. 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): 1529-35. PMID 11087882
15. McLaren GD, Gordeuk VR. Hereditary hemochromatosis: insights from the Hemochromatosis and Iron Overload Screening (HEIRS) Study. Hematology Am Soc Hematol Educ Program. 2009: 195-206. PMID 20008199
16. U.S. Preventive Services Task Force (USPSTF). Hemochromatosis: Screening (inactive). 2006; https://www.uspreventiveservicestaskforce.org/BrowseRec/InactiveTopic/219. Accessed March 23, 2020.

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2012	New policy	
June 2013	Replace policy	Policy updated with literature review. No changes to policy statement.
June 2014	Replace policy	Policy updated with literature review through March 23, 2014; references 1-4, 20-21added; references 16-17 updated. No change in policy statements.
June 2015	Replace policy	Policy updated with literature review through April 1, 2015. References 1, 6 and 23 added. Policy statements unchanged.
September 2018	Replace policy	Policy updated with literature review through March 6, 2018; the reference list was revised and reordered, 6 references were removed, reference 15 added. The policy is revised with updated genetics nomenclature. "Mutations" changed to "variants" in policy statements. Policy statements otherwise unchanged
September 2019	Replace policy	Policy updated with review of guidelines through March 20, 2019; references 14-15 removed; no references added. Policy statement unchanged.
September 2020	Replace policy	Policy updated with literature review and review of guidelines through March 20, 2020; Policy statements unchanged.