

MEDICAL POLICY

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| SUBJECT: GENETIC TESTING FOR HEREDITARY HEMOCHROMATOSIS | EFFECTIVE DATE: 10/18/01 REVISED DATE: 06/20/02, 04/24/03, 03/18/04, 03/17/05, 01/19/06, 01/18/07, 11/15/07 ARCHIVED DATE: 12/18/08 EDITED DATE: 11/19/09, 11/18/10, 11/17/11, 11/15/12, 12/19/13, 10/16/14, 11/19/15, 09/15/16, 09/21/17, 09/20/18 |
| POLICY NUMBER: 2.02.05 CATEGORY: Laboratory Tests | PAGE: 1 OF: 5 |
| <ul style="list-style-type: none">• <i>If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.</i>• <i>If a commercial product (including an Essential Plan product) or a Medicaid product covers a specific service, medical policy criteria apply to the benefit.</i>• <i>If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.</i> | |

POLICY STATEMENT:

- I. Based upon our criteria and review of the peer-reviewed literature, genetic testing for HFE-associated hereditary hemochromatosis (HFE-HHC) has been medically proven to be effective and therefore, **medically appropriate** when offered in a setting with adequately trained health care providers to provide appropriate pre-and post-test genetic counseling and performed by a qualified laboratory for the following indications:
 - A. Confirmatory diagnostic testing of individuals with clinical symptoms of iron overload consistent with HFE-HHC (fasting transferrin saturation value higher than 45%); or
 - B. Carrier testing of:
 1. asymptomatic first-degree relatives of a HFE-HHC proband (genotype: C282Y/C282Y or C282Y/H63D); or
 2. a reproductive partner of a known HFE mutation carrier (both HFE alleles have been identified).
- II. Based upon our criteria and review of the peer-reviewed literature, routine genetic screening for hereditary hemochromatosis in the asymptomatic general population has not been medically proven to be effective and is considered **investigational**.

This policy addresses only *HFE*- associated hereditary hemochromatosis.

POLICY GUIDELINES:

- I. The Health Plan and its employees adhere to all state and federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test.
- II. Coverage of genetic testing is contract dependent.
- III. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).
- IV. Coverage only applies to members with a valid contract. Coverage is not provided for family members without a valid contract.

DESCRIPTION:

HFE-associated hereditary hemochromatosis (HFE-HHC), or primary iron overload, is a disease of iron regulation resulting in excessive iron absorption and, if untreated, may lead to hepatic cirrhosis, diabetes mellitus, cardiomyopathy and other clinical complications. HFE-HHC is one of the most common autosomal recessive disorders among Caucasians of Northern European heritage in the United States. The carrier frequency for a mutant HFE allele in the general population of European origin is approximately 11% or one in every nine persons.

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The two mutations in the HFE gene that are strongly linked to HFE-HHC are C282Y and H63D. H63D is not associated with the same degree of iron overload as C282Y. C282Y homozygous patients have the highest prevalence of HHC-associated iron overload of any genotype. Prevalence is generally higher among males. The frequency of clinical expression of the HFE mutations in terms of the development of iron overload and clinical disease is unclear. There are other hereditary forms of hemochromatosis that are not due to the HFE mutations as well as various acquired or secondary iron overload disorders.

The diagnosis of HFE-HHC in patients with clinical symptoms of iron overload is typically based on blood tests (transferrin saturation and serum ferritin concentration) confirmed by molecular genetic testing for the C282Y and H63D mutations in the HFE gene. Symptomatic individuals who lack the common HFE mutations may have liver disease unrelated to HFE-HHC. Liver biopsy with assessment of histology and hepatic iron concentration is the usual next diagnostic test for these individuals. Limited genetic testing for non-HFE associated hereditary hemochromatosis is available.

RATIONALE:

The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with a high positive predictive value of the occurrence of a disease. Analytical sensitivity and specificity of a genetic test must be of such a level that the test results can and will be used in making treatment decisions. Several large cross-sectional studies have characterized the relationship between identification of the HFE gene mutations and hereditary hemochromatosis, including the magnitude of the association, the sensitivity and specificity of HFE genotyping in identifying hereditary hemochromatosis. There is effective treatment for the management of hereditary hemochromatosis. There is evidence of improved survival with early diagnosis.

Genetic testing of adults with serum transferrin iron saturation greater than 45% can identify individuals homozygous for C282Y mutation or heterozygous for C282Y and H63D mutations who are at risk of developing HFE-HHC. Genetic testing of at-risk family members of probands can be used to identify carriers and noncarriers for the purpose of medical follow-up and potential treatment, as well as life-style and reproductive planning. In addition, due to the approximate 11% of individuals of European origin carrying a HFE mutation, testing of reproductive partners of known carriers provides an opportunity to guide preconception counseling.

Consensus holds that children at risk for adult onset diseases should not have genetic testing in the absence of symptoms. It is generally accepted in the published literature that unless useful medical intervention can be offered to children as a result of testing, formal testing should wait until the child is old enough to understand the consequences of testing and request it for him-or herself.

Population-based genetic screening for HFE-HHC is not recommended at this time because of uncertainties about prevalence and penetrance of HFE mutations in various ethnic groups and the optimal care of asymptomatic people carrying HFE mutations as well as the possible stigmatization and discrimination as a result of genetic testing. The US Preventive Services Task Force (2006) suggests there is currently insufficient evidence to recommend routine genetic screening for hereditary hemochromatosis in the asymptomatic general population based on the following rationale:

- I. There is fair evidence that disease due to hereditary hemochromatosis is rare in the general population.
- II. There is fair evidence that a low proportion of individuals with a high-risk genotype (C282Y homozygote at the HFE locus, a mutation common among white populations presenting with clinical symptoms) manifest the disease.
- III. There is poor evidence that early therapeutic phlebotomy improves morbidity and mortality in screening-detected versus clinically detected individuals.
- IV. Screening could lead to identification of a large number of individuals who possess the high-risk genotype but may never manifest the clinical disease. This may result in unnecessary surveillance, labeling, unnecessary invasive work-up, anxiety, and, potentially, unnecessary treatments.
- V. The potential harms of genetic screening for hereditary hemochromatosis outweigh the potential benefits.

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In 2005, the American College of Physicians published the following recommendations regarding the evidence related to screening for hereditary hemochromatosis:

- I. There is insufficient evidence for or against screening the general population for hemochromatosis.
- II. Transferrin saturation and ferritin levels are the preferred means for case-finding patients with hemochromatosis.
- III. Physicians should counsel patients on the benefits and limitations of genetic screening for hemochromatosis prior to laboratory testing.
- IV. Further research is required to determine better diagnostic, prognostic, and therapeutic data for hemochromatosis.

The Agency for Health Care Guidelines published the diagnosis and management of hemochromatosis: 2011 practice guidelines by the American Association for the Study of Liver Diseases which recommend screening of first-degree relatives of patients diagnosed with *HFE*-related hereditary hemochromatosis (1A, strongly recommends, high quality of evidence). Screening the asymptomatic general population is not recommended because screening could lead to identification of a large number of individuals who possess the high-risk genotype but may never manifest the clinical disease. This may result in unnecessary surveillance and diagnostic procedures, labeling, anxiety, and, potentially, unnecessary treatments.

CODES: Number Description

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

CPT: 81256 *HFE* (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)

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HCPCS: No specific code(s)

ICD10: D64.0-D64.3 Other anemias (code range)
 E83.10-E83.19 Disorders of iron metabolism (code range)
 Z83.2 Family history of diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism

REFERENCES:

Adams PC, et al. (Screening (HEIRS Study Research Investigators). Hemochromatosis and iron-overload screening in a racially diverse population. NEJM 2005 Apr 28;352(17):1769-78.

Andersen RV, et al. Hemochromatosis mutations in the general population: iron overload progression rate. Blood 2004 Apr 15;103(8):2914-9.

Agency for Health Care Guidelines. Guide to preventative services, 2014. Recommendations to the U.S. Preventative Task Force. Hemochromatosis, screening. [<http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/guide/section2b.html#hemo>] accessed 8/29/17.

Barton JC, et al. Initial screening transferrin saturation values, serum ferritin concentrations, and *HFE* genotypes in Native Americans and whites in the Hemochromatosis and Iron Overload Screening Study. Clin Genet 2006 Jan;69(1):48-57.

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BlueCross BlueShield Association, Genetic Testing for Hereditary Hemochromatosis. Medical Policy Reference Manual 2.04.80. 2017 May 08.

*BlueCross BlueShield Association. Evaluation of genetic testing for HFE gene mutations related to hereditary hemochromatosis. Technology Evaluation Center Assessment Program. 2002 Apr;16(22).

*Beutler E, et al. Penetrance of 845GA(C282Y) HFE hereditary haemochromatosis mutation in the USA. Lancet 2002 Jan;359:211-8.

Bryant J, et al. A systematic review of the clinical validity and clinical utility of DNA testing for hereditary haemochromatosis type 1 in at-risk populations. J Med Genet 2008 Aug;45(8):513-8.

Delatycki MB, et al. Use of community genetic screening to prevent HFE-associated hereditary haemochromatosis. Lancet 2005 Jul 23-29;366(9482):314-6.

Ellervik C, et al. Hereditary hemochromatosis genotypes and risk of ischemic stroke. Neurol 2007 Mar 27;68(13):1025-31.

Hannuksela J, et al. Hereditary hemochromatosis gene (HFE) mutations C282Y, H63D and S65C in patients with idiopathic dilated cardiomyopathy. Eur J Heart Fail 2005 Jan;7(1):103-8.

Kowdley K, et al. HFE-associated hereditary hemochromatosis. GeneReviews last update 2015 Sep 17. [http://www.ncbi.nlm.nih.gov/books/NBK1440/] accessed 8/29/17.

McLaren GD, et al. Hereditary hemochromatosis: insights from the Hemochromatosis and Iron Overload Screening (HEIRS) Study. Hematology Am Soc Hematol Educ Program 2009:195-206.

McLaren CE, et al. Hemochromatosis and iron overload screening (HEIRS) study design for an evaluation of 100,000 primary care-based adults. Am J Med Sci 2003 Feb;325(2):53-62.

Nadakkavukaran IM, et al. Screening for hereditary haemochromatosis. Pathology 2012 Feb;44(2):148-52.

National Human Genome Research Institute. Learning about hereditary hemochromatosis. National Institutes of Health (NIH). Updated: 2012 Oct 23 [http://www.genome.gov/10001214#top] accessed 8/29/17.

Pietrangelo A. Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. Gastroenterol 2010 Aug;139(2):393-408.

Pietrangelo A. Molecular insights into the pathogenesis of hereditary haemochromatosis. Gut 2006 Apr;55(4):564-8.

Powell LW, et al. Screening for hemochromatosis in asymptomatic subjects with or without a family history. Arch Intern Med 2006 Feb 13;166(3):294-301.

Qaseem A, et al. Screening for hereditary hemochromatosis: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2005 Oct 4;143(7):517-21.

Schmitt B, et al. Screening primary care patients for hereditary hemochromatosis with transferrin saturation and serum ferritin level: systematic review for the American College of Physicians. Ann Intern Med 2005 Oct 4;143(7):522-36.

*Steinberg KK, et al. Prevalence of C282Y and H63D mutations in the hemochromatosis (HFE) gene in the United States. JAMA 2001;285(17):2216-22.

Task Force on Genetic Testing. Final Report - updated 2006 Apr [http://www.genome.gov/10002393#%20EXECUTIVE] accessed 8/29/17.

*Tavill AS. American Association for the Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association. Diagnosis and management of hemochromatosis. Hepatol 2001;33:1321-8.

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U.S. Preventive Services Task Force. Screening for hemochromatosis: recommendation statement. Ann Intern Med 2006 Aug 1;145(3):204-8.

Whitlock EP, et al. Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2006 Aug 1;145(3):209-23.

* key article

KEY WORDS:

Hereditary hematochromatosis, Primary iron overload, HFE-associated hereditary hemochromatosis, HFE-HHC.

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures. Please refer to the following LCD website for Medicare Members: https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35000&ver=54&CtrctrSelected=298*1&Ctrctr=298&s=41&DocType=Active&bc=AggAAAQIAAAAA%3d%3d&