

## ***Genetic Testing for Hereditary Hemochromatosis***

**Effective:** March 1, 2019

**Next Review:** December 2019

**Last Review:** January 2019

### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

This is a test for pathogenic variants in the *HFE* gene, which are responsible for the majority of clinically significant hereditary hemochromatosis.

### **MEDICAL POLICY CRITERIA**

- I. Genetic testing for *HFE* pathogenic variants may be considered **medically necessary** for either of the following:
  - A. Patients who meet one or both of the following criteria:
    1. Transferrin saturation greater than or equal to 45% in the absence of confounding causes of hyperferritinemia, including but not limited to alcohol abuse, the metabolic syndrome, inflammatory states, or acute and chronic hepatitis
    2. A first-degree relative with hemochromatosis. First-degree relatives include: parents, siblings, and children of an individual.
  - B. A parent whose *HFE* gene variant status is unknown when one parent has known hereditary hemochromatosis and testing is to inform homozygosity or heterozygosity status in a child.

- II. Genetic testing for *HFE* pathogenic variants is considered **not medically necessary** in children with at least one parent with normal *HFE* gene status.
- III. Genetic testing for hereditary hemochromatosis in screening of the general population is considered **investigational**.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

## POLICY GUIDELINES

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
  - History and physical exam including any relevant diagnoses related to the genetic testing
  - Conventional testing and outcomes
  - Conservative treatments, if any

## CROSS REFERENCES

None

## BACKGROUND

Hereditary hemochromatosis (HH), a common genetic disorder of iron metabolism, can lead to excessive iron absorption, toxic accumulation, and organ damage. It is an autosomal recessive disorder; therefore, the same genetic variant must be passed on from both parents (homozygosity) in order for a child to inherit the disease. HH is the most commonly identified genetic disorder in Caucasians, and may be seen in approximately 1 in 250 Caucasians. Untreated HH leads to premature death, usually by liver complications. However, fully expressed disease with end-organ manifestations is seen in <10% of those individuals diagnosed. Treatment by removing excess iron with serial phlebotomy is simple and effective, and if started before irreversible end organ damage, restores normal life expectancy.

Genetic testing is available to assess variants in the *HFE* gene, which are responsible for the majority of clinically significant cases of HH. The majority of patients with HH have variants in the *HFE* gene, which is on the short arm of chromosome 6. Known mutations associated with this gene are:

- C282Y (associated with 60-90% of all HH cases)
- H63D (heterozygosity for C282Y/H63D are associated with iron overload)
- S65C (rare variant, with low penetrance)

HFE-related HH is now frequently identified in asymptomatic probands and in presymptomatic relatives of patients who are known to have the disease.<sup>[1]</sup> Therefore, a genetic diagnosis can be applied to individuals who have not yet developed phenotypic expression. These individuals have a genetic susceptibility to developing iron overload but may never do so.

## REGULATORY STATUS

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were identified. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

## EVIDENCE SUMMARY

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Human Genome Variation Society (HGVS) nomenclature<sup>[2]</sup> is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

## TECHNOLOGY ASSESSMENTS

The 2001 BlueCross BlueShield Technology Evaluation Center (TEC) Assessment on the genetic testing for *HFE* gene variants related to HH concluded the following:<sup>[3]</sup>

- Although randomized controlled trials (RCT) addressing the effect of early phlebotomy therapy in HH patients are limited, studies which assess the predictors of survival in HH patients suggest that survival is improved when phlebotomy therapy is performed adequately, when it is initiated while patients are asymptomatic, before they have progressed to a high degree of iron overload, and before they have developed cirrhosis or diabetes.
- The body of evidence to support genotyping for HH is limited. However, *HFE* genetic testing was found to improve net health outcomes through the identification of low versus high penetrance variants. This *HFE* genotype distinction helps to define the frequency of patient serum marker monitoring. An improvement in patient monitoring could lead to early detection of iron overload in pre-symptomatic patients, which would initiate early phlebotomy treatments.

- Genetic testing and counseling for *HFE* variants may improve outcomes in the management of patients with symptoms of iron overload consistent with hereditary hemochromatosis, in the setting of two consecutive transferrin saturation values of 45% or more and a serum ferritin value of less than 200–300 mcg/L.
- Genetic testing and counseling for *HFE* variants in asymptomatic relatives of individuals with hereditary hemochromatosis also may improve health outcomes.

The Assessment did not address the use of genetic testing for *HFE* gene variants in screening of the general population.

## **ANALYTIC VALIDITY**

A 2016 study published by Press reported data from the College of American Pathologists on their proficiency testing for laboratories performing *HFE* genetic testing.<sup>[4]</sup> A total of 7,663 samples over a 10-year period were graded and analytical error rate, sensitivity and specificity were calculated. Of those samples, 99.3% were determined to have the correct *HFE* analytical test result, with a lower error rate when only North American laboratories were included. The analytical sensitivity and specificity were >98.5% and >99.5%, respectively.

In 2005, Stuhmann<sup>[5]</sup> initiated a pilot study on DNA-based screening of hereditary hemochromatosis in Germany, to study the analytic validity of different test methods. A total of 3,961 individuals provided blood samples for testing of the *HFE* variant C282Y; of these, 3,930 samples were successfully tested with two independent test methods (either polymerase chain reaction [PCR] and restriction digest, reverse allele-specific oligonucleotide hybridization, solid-phase oligonucleotide ligation assay [SPOLA], or microarray [DNA-chip]). In all, 67 of the tested individuals were homozygous for C282Y; 42.6% of the homozygotes already knew their clinical diagnosis of HH before sending the blood sample. Iron accumulation with further signs or symptoms of HH was present in eight of 34 newly diagnosed C282Y homozygous individuals. Of 7,860 tests performed, 7,841 (99.6%) gave correct results. The overall error rate was 0.24% (95% confidence interval [CI]: 0.15–0.38%). The analytic specificity of the tests methods with respect to the detection of homozygosity for C282Y was 100% (7,726 of 7,726 non-homozygous test challenges, 95% CI: 99.95–100%), while the analytic sensitivity was 97% (130 of 134 homozygous test challenges, 95% CI: 92.5–99.2%). The authors concluded that the test methods for C282Y are robust, highly sensitive and specific.

## **CLINICAL VALIDITY**

Although there has never been a randomized controlled trial (RCT) of phlebotomy versus no phlebotomy in the treatment of HH, there is evidence that initiation of phlebotomy before the development of cirrhosis and/or diabetes will significantly reduce the morbidity and mortality of HH.<sup>[1,6,7]</sup> In addition, controlled treatment trials are unlikely due to the health risks which would be associated with the control group. Therefore, high quality observational studies are needed.<sup>[8]</sup>

In 2008, Bryant<sup>[9]</sup> evaluated the clinical validity of HFA genetic testing in people suspected of having hereditary hemochromatosis and in family members of those diagnosed with the disorder by conducting a systematic review of 15 electronic databases. 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 if they reported or allowed the calculation of sensitivity and specificity.

In total, 11 observational studies were included that could be used to evaluate clinical validity of genotyping for the C282Y variant in the diagnosis of HH. Criteria used to define hemochromatosis varied between studies. Clinical sensitivity of C282Y homozygosity for HH 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%.

## CLINICAL UTILITY

In 2009, Picot conducted a systematic review of the psychosocial aspects of DNA testing for HH in at-risk individuals.<sup>[10]</sup> Three observational studies met their inclusion criteria and the authors concluded that, while evidence is limited, the results suggest that genetic testing for HH in at-risk individuals is accompanied by few negative psychosocial outcomes.

As discussed above, Bryant also evaluated the clinical utility of HFA genetic testing in people suspected of having hereditary hemochromatosis and in family members of those diagnosed with the disorder by conduct a systematic review of 15 electronic data bases. No clinical utility studies were found; however, the authors concluded that DNA testing for HH in at-risk populations has clinical validity and may have clinical utility.

## POPULATION SCREENING FOR HEREDITARY HEMOCHROMATOSIS

In a 2016, Barton reported a sub-group analysis of the HEIRS study that sought to identify risk factors for insulin resistance, metabolic syndrome (MetS), and diabetes mellitus in 248 non-Hispanic white *HFE* C282Y homozygous participants.<sup>[11]</sup> Twenty-six C282Y/C282Y participants (10.5%) had diabetes diagnoses. HOMA-IR fourth quartile was positively associated with age ( $p = 0.0002$ ); male sex ( $p = 0.0022$ ); and BMI ( $p < 0.0001$ ) in homozygous participants; and HOMA-IR fourth quartile predicted metabolic syndrome (MetS) ( $p < 0.0001$ ). Diabetes, in this sub-group was positively associated with age ( $p = 0.0012$ ); male sex ( $p = 0.0068$ ); MP joint hypertrophy ( $p = 0.0167$ ); neutrophils ( $p = 0.0342$ ); and MetS ( $p = 0.0298$ ). Serum ferritin levels were not found to be predictive of any of the outcomes analyzed, including HOMA-IR fourth quartile, MetS, or diabetes.

In a 2013 sub-study of Caucasian participants in the HEIRS study, Adams assessed the prevalence of *HFE* variants in patients who had elevated serum ferritin levels less than 1000 mcg/L (300-1000 mcg/L for men and 200-1000 mcg/L for women).<sup>[12]</sup> Among 3359 men and 2416 women, prevalence of potential iron-loading *HFE* genotypes (defined as C282Y homozygote, C282Y/H63D compound heterozygote, or H63D homozygote) was 10% and 12% in men and women, respectively. Prevalence of C282Y homozygosity was 2% and 4% among men and women, respectively. Likelihood of C282Y homozygosity increased with increasing serum ferritin levels, from 0.3% to 16% in men, and from 0.3% to 30% in women. Post-test likelihood ratios (likelihood of C282Y homozygosity given a positive test result) exceeded 1 at serum ferritin levels of 500 mcg/L or more for men and at levels greater than 300 mcg/L for women. In Caucasian individuals with mild hyperferritinemia, causes of elevated serum ferritin level other than C282Y or H63D *HFE* variants (e.g., liver disease, diabetes) were more likely.

In 2009, McLaren and Gordeuk 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 multi-ethnic, primary care-based sample of 101,168 adults enrolled over a two year period at four centers in the U.S. and one in Canada.<sup>[13]</sup> Initial screening of the participants included genotyping for the *HFE* C282Y and H63D alleles, serum ferritin, and a calculated transferrin

saturation. The yield of *HFE* genotyping in identifying persons with C282Y homozygosity was low in racial/ethnic groups other than non-Hispanic Caucasians. The overall frequency homozygosity for the C282Y variant in non-Hispanic Caucasians was 4.4 per 1,000. There was marked heterogeneity of disease expression in C282Y homozygotes. The authors concluded that 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 who may benefit from continued monitoring of iron status, and that, 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 is not recommended.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

In a 2011 practice guideline, the American Association for the Study of Liver Disease (AASLD) recommends:<sup>[1]</sup>

- "...patients with abnormal iron studies should be evaluated as patients with hemochromatosis, even in the absence of symptoms (strength of recommendation A by the classification used by the Grading of Recommendation Assessment, Development, and Evaluation [GRADE] workgroup)."
- "In a patient with suggestive symptoms, physical findings, or family history of HH, a combination of transferrin saturation and ferritin should be obtained rather than relying on a single test, and if either is abnormal (transferrin saturation  $\geq 45\%$  or ferritin above the upper limit of normal), then *HFE* mutation analysis should be performed. (Strength of recommendation 1B; Strong; Quality of Evidence: Moderate. Further research may change confidence in the estimate of the clinical effect.)"
- "...screening (iron studies and *HFE* mutation analysis) of first-degree relatives of patients with *HFE*-related HH to detect early disease and prevent complications. (Strength of recommendation 1A; Strong; Quality of Evidence: High. Further research is unlikely to change confidence in the estimate of the clinical effect.)"
- Screening for non-*HFE*-related HH is not recommended. Average risk population screening for HH is not recommended. (Strength of recommendation 1B; Strong; Quality of Evidence: Moderate. Further research may change confidence in the estimate of the clinical effect.)

### U.S. PREVENTIVE SERVICES TASK FORCE

In 2006, the U.S. Preventative Task Force (USPSTF) released an evidence-based clinical guideline on screening for hemochromatosis.<sup>[14]</sup> The guideline recommends against routine screening for hereditary hemochromatosis in the asymptomatic general population, stating, "The USPSTF concludes that the potential harms of genetic screening for hereditary hemochromatosis outweigh the potential benefits."

## SUMMARY

There is enough research to show that genetic testing for *HFE* gene pathogenic variants may lead to improved health outcomes and restoration of normal life expectancy. In addition, clinical guidelines based on research recommend that genetic testing for *HFE* gene variants in select patients with abnormal serum iron indices indicating iron overload (transferrin

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saturation  $\geq 45\%$ ), as well as in individuals with a family history of hemochromatosis. Therefore, genetic testing for *HFE* gene variants may be considered medically necessary for select patients with abnormal serum iron indices indicating iron overload (transferrin saturation  $\geq 45\%$ ), as well as in individuals with a family history of hemochromatosis when policy criteria are met.

There is not enough research to show that genetic testing for *HFE* gene variants improves health outcomes in children with at least one parent with normal *HFE* gene status. In addition, no clinical guidelines based on research recommend genetic testing for *HFE* gene variants in children with at least one parent with normal *HFE* gene status. Therefore, genetic testing for *HFE* pathogenic variants is considered not medically necessary in children with at least one parent with normal *HFE* gene status

There is not enough research to show that genetic testing for *HFE* gene variants is suitable for screening of the general public. Although hereditary hemochromatosis is common, the penetrance of the genotype is low, and the natural history of untreated individuals cannot be predicted. In addition, no clinical guidelines based on research recommend genetic testing for *HFE* gene variants for screening purposes. Therefore, genetic testing for hereditary hemochromatosis in screening of the general population is considered investigational.

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## CODES

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

**Date of Origin:** December 2012