Genetic Testing for Hereditary Hemochromatosis

Description

Hereditary hemochromatosis (HH), a common genetic disorder of iron metabolism, can lead to inappropriate iron absorption, toxic accumulation and organ damage. Genetic testing is available to assess mutations in the *HFE* gene, which are responsible for the majority of clinically significant cases of hereditary hemochromatosis.

Background

Iron Overload

Iron overload syndromes may be hereditary, secondary to some other 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 left 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 (either with symptomatic cardiac failure or arrhythmias).

Hereditary hemochromatosis (HH), an autosomal recessive disorder, is the most common, identified, genetic disorder in Caucasians, and may be seen in approximately 1 in 250 Caucasians. However, fully expressed disease with end-organ manifestations is seen in <10% of those individuals. The factors that influence phenotypic expression of *HFE*-related HH (that is the clinical appearance of iron overload) are not clearly defined. The low clinical penetrance appears to be due to a complex interplay of genetic status and other factors such as age, sex, environmental influences and the presence of other diseases.

HH 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. Treatment by removing excess iron with serial phlebotomy is simple and effective, and if started before irreversible end organ damage, restores normal life expectancy.
Diagnosis of Hemochromatosis

Patients with hemochromatosis may present with nonspecific systemic symptoms, specific organ-related symptoms, or they may be asymptomatic. The 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 in the past to confirm diagnosis but is now generally limited to determining the degree of hepatic fibrosis and cirrhosis during management of the disease.

Genetic testing can confirm a hereditary nature of the iron overload.

Genetics of Hereditary Hemochromatosis

The majority of patients with HH have mutations in the HFE gene, which is on the short arm of chromosome 6. The HFE gene was identified and cloned in 1996. The most common mutation in the HFE gene is C282Y, a missense mutation that substitutes a cysteine residue for tyrosine at amino acid position 282 on the HFE protein. Homozygosity for the C282Y mutation is associated with 60-90% of all cases of HH. Additionally, 3-8% of individuals affected with HH are heterozygous for this mutation. Penetrance for elevated serum iron indices among C282Y homozygotes is relatively high, but not 100%. However, the penetrance for the characteristic clinical endpoints (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 mutation. (1)

The other significant mutation is referred to as H63D which results in the substitution of aspartic acid for histidine at position 63. Homozygosity for H63D is insufficient to cause clinically significant iron overload in the absence of modifying factors. However, heterozygosity for C282Y/H63D has been associated with increased hepatic iron concentrations; approximately 1-2% of patients with this genotype will develop clinical evidence of iron overload, usually in the presence of another liver disease. (2)

The clinical significance of a third HFE mutation, S65C, appears to be minimal. This rare variant displays very low penetrance. Compound heterozygosity for C282Y and 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 mutations in HFE and in non-HFE genes (eg, transferrin receptor 2, TFR2) resulting in iron overload syndromes are rare. (3-6)

With the advent of genetic testing in the late 1990s, HFE-related HH is now frequently identified in asymptomatic probands and in presymptomatic relatives of patients who are known to have the disease. (7) 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. A consensus conference of the European Association for the Study of Liver Diseases
in 2000 led to a recognition of the different stages and progression of hemochromatosis. These stages were defined as:

1. Stage 1: those patients with the genetic disorder with no increase in iron stores who have "genetic susceptibility".
2. Stage 2: those patients with the genetic disorder who have phenotypic evidence of iron overload but who are without tissue or end organ damage.
3. Stage 3: those individuals who have the genetic disorder with iron overload and have iron deposition to the degree that tissue and end organ damage occurs.

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. 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.

Related Policies

None

Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Genetic testing for HFE gene mutations may be considered medically necessary in a patient with abnormal serum iron indices indicating iron overload. (See Policy Guidelines)

Policy Guidelines

Serum Iron Indices in the Diagnosis of HH

Elevated fasting transferrin saturation (the ratio of serum iron to total iron-binding capacity) is the most sensitive initial phenotypic screening test. A cut-off 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 confounding causes of hyperferritinemia (alcohol abuse, the metabolic syndrome, inflammatory states and acute and chronic hepatitis), serum ferritin is a good marker of the degree of iron overload. (8)

The negative predictive value of a normal transferrin saturation and serum ferritin is 97%. In this situation, no further testing is recommended. (8)
2011 Practice Guidelines by the American Association for the Study of Liver Diseases recommend *HFE* gene mutation testing in patients with abnormal serum iron indices, even in the absence of symptoms (e.g., abnormal serum iron indices on routine screening chemistry panel).

**Rationale**

**Literature Review**

Recent reviews highlight the pathogenesis, diagnosis and management of HH. (8-11)

A 2001 Blue Cross and Blue Shield Technology Evaluation Center (TEC) Assessment on the genetic testing for *HFE* gene mutations related to HH concluded the following:

- genetic testing and counseling for *HFE* mutations in the management of patients with symptoms of iron overload consistent with hereditary hemochromatosis, in the setting of 2 consecutive transferrin saturation values of 45% or more and a serum ferritin value of less than 200–300 mcg/L, met the TEC criteria.

The Assessment did not address the use of genetic testing for *HFE* gene mutations in screening of the general population. (12)

Validation of the clinical use of any genetic test focuses on 3 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.

**Analytic validity**

Stuhrmann and colleagues (13) initiated a pilot study on DNA-based screening of hereditary hemochromatosis in Germany. One of the major aspects of the study was the analytic validity of different test methods. A total of 3,961 individuals provided blood samples for testing of the HFE mutation 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 8 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

Bryant and colleagues (14) evaluated the clinical validity and clinical utility of DNA testing in people suspected of having hereditary hemochromatosis by conducting a systematic review of 15 electronic databases (including MEDLINE and the Cochrane library) up to April 2007. 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. Clinical utility studies were included if they reported the use of DNA tests in Caucasians with iron overload suggestive of HH compared with any case-identification strategy not involving DNA, and had to report patient-based outcomes (such as morbidity or mortality).

Eleven observational studies that could be used to evaluate clinical validity of genotyping for the C282Y mutation in the diagnosis of HH were identified. 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%. The authors concluded that DNA testing for HH in at-risk populations has clinical validity and may have clinical utility.

Clinical utility

The clinical utility of genetic testing for HH depends on how the results can be used to improve patient management. Although there has never been a randomized controlled trial of phlebotomy versus no phlebotomy in 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. (7, 15,16)

Data exists on the psychosocial aspect of genetic testing for HH. Picot and colleagues conducted a systematic review of the psychosocial aspects of DNA testing for HH in at-risk individuals. (17) Databases were searched through 2007 for any quantitative or qualitative primary research that considered DNA testing of individuals considered at-risk of HH and reported psychosocial outcomes. Three observational studies met their inclusion criteria; each had methodologic limitations. After receiving test results, patient anxiety levels fell or were unchanged, general health-related quality of life outcomes improved in some aspects, or were unchanged with respect to pretest results. Outcomes were not reported separately for those referred for diagnosis and those with family history of HH. 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.

Population screening for HH

General population screening for HH has been proposed because of the high prevalence of the disease, the lack of early clinical findings/nonspecific early clinical findings, the specificity of the findings once they appear, the low cost of diagnosis and treatment, and the high cost and low success rate of late diagnosis and treatment. However, because the penetrance of the genotype is low, and the natural
history of untreated individuals cannot be predicted, there is a lack of support for population-based screening. The American Academy of Family Physicians, Centers for Disease Control and Prevention, and U.S. Preventive Services Task Force recommend against population-based general screening. (18-20)

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 2-year period at 4 centers in the U.S. and one in Canada. (21) Initial screening of the participants included genotyping for the \textit{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 mutation 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.

In a substudy of Caucasian participants in the HEIRS study, Adams et al (2013) assessed the prevalence of \textit{HFE} mutations in patients who had elevated serum ferritin levels less than 1000 mcg/L (300-1000 mcg/L for men, 200-1000 mcg/L for women). (22) Among 3359 men and 2416 women, prevalence of potential iron-loading \textit{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 subjects with mild hyperferritinemia, causes of elevated serum ferritin level other than C282Y or H63D \textit{HFE} mutations (eg, liver disease, diabetes) were more likely.

\textbf{Clinical Trials}

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

\textbf{Practice Guidelines and Position Statements}

\textbf{American Academy of Family Physicians}

AAFP recommends against routine genetic screening for hereditary hemochromatosis in the asymptomatic general population. (Grade D recommendation: at least fair evidence that [the service] is ineffective or that harms outweigh benefits) (18)
American Association for the Study of Liver Diseases

A 2011 practice guideline from AASLD recommends (7):

- Patients with abnormal iron studies should be evaluated as patients with hemochromatosis, even in the absence of symptoms (based on high quality evidence [A]).
- 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 ≥45% or ferritin above the upper limit of normal), then HFE mutation analysis should be performed (strength of recommendation 1 [strong] by the classification of the Grading of Recommendation Assessment, Development, and Evaluation [GRADE] workgroup; based on moderate quality evidence [B]).
- Screening (iron studies and HFE mutation analysis) of first-degree relatives of patients with HFE-related HH is recommended to detect early disease and prevent complications. (1A)
- Screening for non-HFE-related HH is not recommended. Average risk population screening for HH is not recommended. (1B)

Centers for Disease Control and Prevention

CDC does not currently recommend population screening for HFE mutations. (19)

U.S. Preventive Services Task Force

The U.S. Preventive Services Task Force has decided not to review the evidence and update its recommendations for hemochromatosis screening. 23

Summary

Hereditary hemochromatosis is a common genetic disorder in the Caucasian population. Testing for mutations in the HFE gene, which contributes to the majority of cases of hereditary hemochromatosis, can confirm a genetic etiology; if clinically indicated, serial phlebotomy may be initiated, which can lead to a restored normal life expectancy. Therefore, genetic testing for HFE gene mutations may be considered medically necessary for patients with a clinical suspicion of hemochromatosis (signs and symptoms of iron overload) or in patients with fasting serum iron indices that are suggestive of iron overload.

Medicare National Coverage

No national coverage determination.

References


19. Centers for Disease Control and Prevention. Hemochromatosis (iron storage disease). Training & education - epidemiology prevalence. Available online at:


