HFE Hemochromatosis Genetic Testing

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Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
HFE Targeted Mutation Analysis (common variants)	81256
HFE Sequence Analysis	81479
HFE Deletion/Duplication Analysis	81479

Criteria

Introduction

Requests for HFE hemochromatosis genetic testing are reviewed using the following criteria.

HFE known familial mutation testing

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing of the HFE gene that would detect the known familial mutation, AND
- Presymptomatic/Asymptomatic Genetic Testing:
  - HFE mutation(s) identified in 1st degree biological relative, OR
- Diagnostic Testing:
  - HFE mutation(s) identified in 1st degree biological relative, and
  - Serologic evidence of iron overload (e.g., a transferrin saturation greater than or equal to 45% and/or elevated ferritin), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

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HFE targeted mutation testing

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing of the HFE gene, AND
- Presymptomatic/Asymptomatic Genetic Testing:
  - Documented family history of first-degree relative with HFE hemochromatosis, OR
- Diagnostic Testing:
  - Serologic evidence of iron overload (e.g., transferrin saturation greater than or equal to 45% and/or elevated ferritin), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

HFE gene sequence analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous sequencing of the HFE gene, and
  - Previous targeted HFE genetic testing performed and zero or one mutation identified, AND
- Diagnostic Testing:
  - Serologic evidence of iron overload (e.g., transferrin saturation greater than or equal to 45% and/or elevated ferritin), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

HFE deletion/duplication analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous deletion/duplication analysis of the HFE gene, and
  - Previous HFE sequencing performed and zero or one mutation identified, AND
- Diagnostic Testing:
  - Serologic evidence of iron overload (e.g., transferrin saturation greater than or equal to 45% and/or elevated ferritin), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

What is HFE hemochromatosis?

HFE hemochromatosis is a disorder marked by high absorption of iron by the mucosa of the small intestine.[1]

Prevalence

About 1 in 200 to 1 in 400 non-Hispanic whites in North America are affected with HFE hemochromatosis.[2] The disorder is less common among Blacks, Hispanics and Asians in North America.[1]

Symptoms

There is a phenotypic spectrum of HFE hemochromatosis.[1]

- Clinical HFE hemochromatosis: individuals manifest end-organ damage secondary to iron overload.
- Biochemical HFE hemochromatosis: individuals have increased transferrin-iron saturation and serum ferritin but no clinical features of iron overload.[1]
- Non-expressing C282Y homozygotes: individuals with two copies of the HFE mutation C248Y have neither clinical manifestations of disease nor iron overload.

Individuals who are untreated may experience the following symptoms: abdominal pain, weakness, lethargy, weight loss, arthralgias, diabetes mellitus, and increased risk of cirrhosis when the serum ferritin is higher than 1,000 ng/mL.[1] Other findings may include progressive increase in skin pigmentation, congestive heart failure, and/or arrhythmias, arthritis, and hypogonadism.[1] Clinical HFE hemochromatosis is more common in men than women.[1]

HFE hemochromatosis is typically an adult-onset condition.[1] Juvenile forms of hereditary hemochromatosis exist, but are caused by other genes, and testing for these forms of hemochromatosis is not addressed by this guideline.

Cause

HFE hemochromatosis is caused by pathogenic mutations in the HFE gene that lead to excess iron absorption and storage in the liver, heart, pancreas, and other organs.[1]

There are other, rarer forms of inherited primary iron overload, but testing for these disorders is not addressed by this guideline. Some of these disorders and their associated genes include:[1]

- BMP6-related iron overload (BMP6)
- Aceruloplasminemia (CP)
- Juvenile hemochromatosis (HAMP, HJV)
- SLC40A1-related hemochromatosis (SLC40A1)

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- TFR2-related hemochromatosis (TRF2)

Hemochromatosis may also be caused by pathogenic mutations in 2 different hemochromatosis-related genes.[1]

Inheritance

HFE hemochromatosis is inherited in an autosomal recessive manner.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

Diagnosis

When HFE hemochromatosis is suspected, serum iron studies, including transferrin saturation (TS), serum ferritin (SF), and unsaturated iron-binding capacity (UIBC), are the first step in establishing a diagnosis. HFE genetic testing is recommended if TS is greater than or equal to 45%.[3,4]

Current guidelines support HFE genetic testing in individuals with: [2,4,5]

- Serologic evidence of iron overload, considered to be a transferrin saturation greater than or equal to 45% and elevated ferritin
- A known family history of hemochromatosis
- A known family mutation in the HFE gene in a first degree relative

Common changes in the HFE gene associated with HFE hemochromatosis are C282Y, H63D, and S65C.[1] C282Y and H63D are the most common changes associated with HFE-related hemochromatosis in those of northern European ancestry:[1]

- C282Y homozygosity: 60-90%
- H63D homozygosity: 1%
- C282Y/H63D compound heterozygosity: 3-8%

There is controversy over whether the H63D variant causes clinical disease.[2,6] The next most common cause are individually rare mutations.[7] S65C has a lower population frequency and may rarely cause HFE hemochromatosis.[8] The combination of these mutations determines both the chances of symptoms occurring and their severity.

Management

HFE hemochromatosis can be effectively treated in most people. Phlebotomy therapy can alleviate almost all symptoms of iron overload if initiated before organ damage occurs.[9]

Survival

Untreated HFE hemochromatosis may result in reduced lifespan due to congestive heart failure and other cardiac manifestations, end-stage liver disease, liver cancer, or extrahepatic cancers.[1]

Test information

Introduction

Testing for HFE hemochromatosis may include known familial mutation analysis, targeted mutation analysis, next-generation sequencing, or deletion/duplication analysis.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon

boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

HFE sequencing and deletion/duplication analysis may be necessary for individuals who do not have northern European ancestry.[1]

Guidelines and evidence

American Association for the Study of Liver Disease

The American Association for the Study of Liver Diseases (AASLD, 2011) Practice Guidelines stated:[5]

- "In a patient with suggestive symptoms, physical findings, or family history, a combination of transferrin saturation (TS) and ferritin should be obtained rather than relying on a single test. (1B) If either is abnormal (TS ≥45% or ferritin above the upper limit of normal), then HFE mutation analysis should be performed. (1B)"
- "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."

American College of Gastroenterology

The American College of Gastroenterology (ACG, 2019) Clinical Guideline on Hereditary Hemochromatosis (called HH in this document) stated:[4]

- "We recommend that family members, particularly first-degree relatives, of patients diagnosed with HH should be screened for HH (strong recommendation, moderate quality of evidence)."
- "We recommend that individuals with the H63D or S65C mutation in the absence of C282Y mutation should be counseled that they are not at increased risk of iron overload (conditional recommendation, very low quality of evidence)."
- "We suggest against further genetic testing among patients with iron overload who tested negative for the C282Y and H63D alleles (conditional recommendation, very low quality of evidence)."
- "[G]enotyping for HFE mutations (C282Y) is now a standard part of the evaluation of patients in whom HH is suspected on clinical grounds or based on the finding of elevated iron studies."

- "We suggest against further genetic testing among patients with iron overload testing negative for the C282Y and H63D alleles (conditional recommendation, very low quality of evidence)."

European Association for the Study of the Liver

The European Association for the Study of the Liver (EASL, 2022) Clinical Practice Guidelines on haemochromatosis stated:[9]

- "Individuals with clinical and biochemical signs of haemochromatosis, elevated transferrin saturation and high serum ferritin concentration, or otherwise unexplained persistently elevated transferrin saturation should be genetically tested for haemochromatosis after informed consent for genetic testing has been obtained (level of evidence 2, strong recommendation, strong consensus)."
- "Adult individuals with a positive family history of first-degree relatives with haemochromatosis should be genetically tested for haemochromatosis after informed consent for genetic testing has been obtained (level of evidence 4, strong recommendation, strong consensus)."
- "Young individuals with biochemical evidence and clinical manifestations of haemochromatosis (liver disease, amenorrhea, hypogonadism, cardiomyopathy) should be tested for rare haemochromatosis gene variants (LoE 4, strong recommendation, strong consensus)."

International Society for the Study of Iron in Biology and Medicine

The International Society for the Study of Iron in Biology and Medicine (BIOIRON Society, 2022) hemochromatosis classification update and recommendations stated:[10]

- "If an appropriately investigated patient has an unequivocal HC [hemochromatosis] phenotype without cofactors but is not a p.Cys282Tyr homozygote (and this includes compound p.Cys282Tyr and p.His63Asp heterozygosity or p.His63Asp homozygosity), a provisional diagnosis of "molecularly undefined" HC can be made, and phlebotomies started."
- "The panelists agree that, whenever possible, an accurate molecular characterization remains important in these patients, especially for cascade screening of asymptomatic siblings or other first-degree relatives. To this end, patients should be referred (or DNA should be sent) to a specialized center. Indeed, second-level genetic tests have limitations that include costs, time delay, and poor availability in certain regions and require a high level of expertise for interpretation."

Note:

This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for HFE hemochromatosis testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For

those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

References

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