



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Genetic Testing for Hereditary Hemochromatosis

Effective Date 2/15/2010
Next Review Date 2/15/2012
Coverage Policy Number 0279

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Hyperlink to Related Coverage Policies

Genetic Counseling
Genetic Testing of Heritable Disorders

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers genetic testing for HFE-associated hereditary hemochromatosis (HHC) as medically necessary when ANY of the following criteria is met:

- For diagnostic testing when the individual has findings consistent with hemochromatosis and serum transferrin iron saturation greater than or equal to 45%, but the diagnosis remains uncertain after completion of conventional testing
- For predictive testing when there is an affected family member (first- or second-degree relative*) who has HHC (both HFE alleles have been identified)
- For carrier testing when the individual is a reproductive partner of a known carrier (both HFE alleles have been identified) and the couple has the capacity and intention to reproduce

*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings and children.

*A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half siblings.

All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a physician or a licensed or certified genetic counselor.

CIGNA does not cover genetic testing for hemochromatosis in the general population, because such screening is considered not medically necessary or of unproven benefit.

General Background

HFE-associated hereditary hemochromatosis (HHC), the most common identified genetic disorder in the Caucasian population of Northern European origin, is an autosomal recessive disease characterized by an abnormally high absorption of iron by the gastrointestinal mucosa. This high absorption leads to excess storage of iron, particularly in the liver, skin, pancreas, heart, joints, and testes. If untreated, hepatic fibrosis, hepatocellular carcinoma, cirrhosis, increased skin pigmentation, diabetes mellitus, congestive heart failure and/or arrhythmias, arthritis, and hypogonadism may develop (King and Barton, 2006; Kowdley, et al., 2006).

The diagnosis of individuals with clinical symptoms consistent with HFE-HHC and/or biochemical evidence of iron overload is typically based on transferrin saturation and serum ferritin blood levels. A fasting transferrin iron saturation of 45% or higher in the absence of other known causes of iron overload is considered suggestive of HFE-HHC and may warrant genetic mutation analysis. Historically, liver biopsy was the standard method used for confirming the diagnosing of HFE-HCC. However, because of its invasive nature and risk, genetic testing has replaced liver biopsy, which is now used more selectively for the assessment of hepatic fibrosis, cirrhosis, and hepatic iron content (Bryant, et al., 2008; Olynyk, et al., 2008; Yen, et al., 2006; Qaseem, et al., 2005).

Up to 90% of United States Caucasians with hemochromatosis have been found to have C282Y/C282Y homozygosity and 2%–5% have C282Y/H63D heterozygosity. A 100% positive predictive accuracy in HHC gene testing has been reported in C282Y homozygotes with an elevated transferrin saturation. Reported sensitivity ranged from 72.2%–100% when analysis was limited to studies that clearly and appropriately defined HHC and were generalizable. Specificity ranged from 98.8%–100%. However, not all individuals with iron overload exhibit a C282Y or H63D mutation. Clinical expression is variable and a significant portion of individuals with these genotypes do not exhibit a specifically defined manifestation of HHC (i.e., low penetrance). Other causes of iron overload (e.g., alcohol consumption, hepatitis C, hyperferritinemia) are ruled out prior to making a diagnosis of HFE-HHC (Bryant, et al., 2009; McLaren and Gordeuk, 2009; King and Barton, 2006; Kowdley, et al., 2006; Tavill, 2001).

Predictive testing may be offered to asymptomatic individuals with a family history of HFE-HHC who are at risk for developing the disease. Offsprings of an individual with HFE-HHC typically inherit one mutant HFE allele from the affected parent. The genetic risk of having HFE-HHC for siblings of a proband is approximately 25%. However, the high carrier frequency for a mutant HFE allele means that one parent may have two abnormal HFE alleles in the absence of clinical findings. In this case, the risk for siblings of a proband being a homozygote for HFE-HHC is 50%. If the results of the testing are positive, intermittent serum ferritin concentrations and transferrin-iron saturation levels may be measured periodically to follow the progression of the disease, allowing for early medical intervention when indicated (Kowdley, et al., 2006).

If both HFE alleles can be identified in a proband, molecular genetic testing can be used to identify carriers and noncarriers in at-risk family members. Testing of asymptomatic adult siblings and offsprings can be done by serum iron studies (phenotype) or by HFE mutation analysis (genotype). Although genotype-based testing has a high negative predictive value, it also has a low positive predictive value because many of the individuals identified with the homozygous or compound heterozygous mutation will not express the disease. Carrier testing may be requested by individuals as part of reproductive planning. Although prenatal testing would be technically feasible when both parents carry identified HFE mutations, such requests would be highly unusual because HFE-HHC is an adult-onset, treatable disease, and there is low clinical penetrance of the homozygous C282Y mutation. Testing for children and adults who have no symptoms is not recommended (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDKD], 2007; Kowdley, et al., 2006).

General population screening has been proposed because of the high prevalence of the disease, the lack of early clinical findings and 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 appears low, and the natural history of untreated individuals cannot be predicted, there is a lack of recommendations for population-based screening. Since it cannot currently be predicted who will develop significant clinical disease, the psychological and social implications of only individuals with early disease who have the biochemical phenotype need to be considered. There is general consensus that genetic screening for HFE-HHC in asymptomatic individuals is not warranted (McLaren and Gordeuk, 2009; Olynyk, et al., 2008; NIDDKD, 2007; King and Barton, 2006; Kowdley, et al., 2006; Beutler, et al., 2003).

McLaren and Gordeuk (2009) 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 adult population (n=101,168). Initial screening of participants included HFE C282Y and H63D genotyping, measurement of serum ferritin levels, unsaturated iron-binding capacity, and calculation of transferrin saturation. The results indicated that the yield of HFE genotyping in C282Y homozygosity individuals is low in racial/ethnic groups other than non-Hispanic Caucasians. C282Y homozygosity was found in 4–5 of every 1000 persons of northern European descent. The authors concluded that “although genetic testing is well accepted and associated with a minimal risk of discrimination, generalized population screening in a primary care population as performed in the HEIRS Study is not recommended”.

Professional Societies/Organizations

In their 2006 statement, the U.S. Preventive Services Task Force (USPSTF) recommended against routine screening for hereditary hemochromatosis in the asymptomatic general population stating that the potential harm outweighs the potential benefits. The USPSTF found 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”. They also stated that there was poor evidence that early intervention improves morbidity and mortality, and that screening could identify a large population of individuals that would never clinically manifest the disease. This recommendation did not apply to individuals with signs and symptoms that would include hereditary hemochromatosis in the differential diagnosis or to individuals who have a family history of clinically-detected or screening-detected probands for hereditary Hemochromatosis.

The American College of Physicians clinical practice guidelines (Qaseem, et al., 2005) on screening for hereditary hemochromatosis included the following four recommendations:

- “There is insufficient evidence to recommend for or against screening for hereditary hemochromatosis in the general population.
- In case-finding for hereditary hemochromatosis, serum ferritin and transferrin saturation tests should be performed.
- Physicians should discuss the risks, benefits, and limitations of genetic testing in patients with a positive family history of hereditary hemochromatosis or those with elevated serum ferritin level or transferrin saturation.
- Further research is needed to establish better diagnostic, therapeutic, and prognostic criteria for hereditary hemochromatosis”.

The committee stated that decisions regarding screening are difficult due to the variable penetrance of mutations of the HFE gene.

The 2001 guidelines by the American Association for the Study of Liver Diseases (Tavill, 2001) recommended that initial screening of individuals with suspected iron overload and those over the age of 20 years who are first-degree relatives of known cases of HHC should be performed by transferrin saturation measurement. They also stated that genotyping to detect HFE mutations should be performed for all individuals who have abnormal iron studies (transferrin saturation of $\geq 45\%$ and elevated serum ferritin) and on those who are first-degree relatives of identified homozygotes.

Summary

The evidence in the published peer-reviewed literature and professional societies supports the use of genetic testing to aide in the diagnosis of HFE hereditary hemochromatosis (HHC) in a subset of individuals who have a serum transferrin iron saturation level greater than or equal to 45% and a diagnosis of HFE-HHC using conventional testing is inconclusive. Predictive testing is indicated when there is a first- or second-degree relative with HHC (both HFE alleles have been identified). Carrier testing may be performed when an individual is a reproductive partner of a known carrier (both HFE alleles have been identified) and the couple has the capacity and intention to reproduce. The need for general population screening has not been established.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

| CPT ^{®*} Codes | Description |
|----------------------------|--|
| 83890 | Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA) |
| 83891 | Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA) |
| 83892 | Molecular diagnostics; enzymatic digestion, each enzyme treatment |
| 83894 | Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide), each nucleic acid preparation |
| 83896 | Molecular diagnostics; nucleic acid probe, each |
| 83898 | Molecular diagnostics; amplification, target, each nucleic acid sequence |
| 83900 | Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences |
| 83901 | Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure) |
| 83903 | Molecular diagnostics; mutation scanning, by physical properties (eg, single strand conformational polymorphisms [SSCP], heteroduplex, denaturing gradient gel electrophoresis [DGGE], RNA'ase A), single segment, each |
| 83909 | Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation |
| 83912 | Molecular diagnostics; interpretation and report |
| 83914 | Mutation identification by enzymatic ligation or primer extension, single segment, each segment (eg, oligonucleotide ligation assay [OLA], single base chain extension [SBCE], or allele-specific primer extension [ASPE]) |
| | Multiple/varied |

| HCPCS Codes | Description |
|----------------|---|
| S3837 | Complete gene sequence analysis for hemochromatosis genetic testing |

| ICD-9-CM Diagnosis Codes | Description |
|--------------------------------|------------------------------|
| 275.0 | Disorders of iron metabolism |

*Current Procedural Terminology (CPT[®]) © 2010 American Medical Association: Chicago, IL.

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Policy History

| <u>Pre-Merger Organizations</u> | <u>Last Review Date</u> | <u>Policy Number</u> | <u>Title</u> |
|-------------------------------------|-----------------------------|--------------------------|--|
| CIGNA HealthCare | 2/15/2008 | 0279 | Genetic Testing for Hereditary Hemochromatosis |

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