Genetic Testing for Hereditary Hemochromatosis

Description of Procedure or Service

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

Iron overload
Iron overload syndromes may be hereditary, secondary to another 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, with an estimated prevalence of 1 in 250. However, fully expressed disease with end-organ manifestations is seen in <10% of affected 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 to confirm diagnosis, but is now generally limited to determining the degree of hepatic fibrosis and cirrhosis during management of the disease. Most patients with a diagnosis of hemochromatosis will exhibit a familial pattern, thereby confirming the diagnosis of HH. However the familial pattern may not be obvious due to the large percentage of undiagnosed patients in some families, and further evaluation of family members may be required to establish whether a familial pattern is present.
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General population screening for HH has been proposed because of the high prevalence of disease, absence of or nonspecific early clinical findings, specificity of findings once they appear, low cost of diagnosis and treatment, and high cost and low success rate of late diagnosis and treatment. However, because penetrance is low, and the natural history of asymptomatic individuals is unpredictable, support for population-based screening is lacking. A U.S. Preventive Services Task Force (USPSTF) review of the literature suggested that up to 38% to 50% of individuals with C282Y homozygotes may develop iron overload, with up to 10% to 33% eventually developing hemochromatosis-associated morbidity.

Treatment of HH
The main treatment modality for patients with HH is periodic phlebotomy. While there has never been a randomized controlled trial of phlebotomy versus no phlebotomy in the treatment of HH, there is evidence from nonrandomized studies that initiation of phlebotomy before the development of cirrhosis and/or diabetes will significantly reduce HH-associated morbidity and mortality.

Genetics of hereditary hemochromatosis
The majority of patients with HH have variants 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 variant in the HFE gene is C282Y, a missense variant that changes cysteine at position 282 in the HFE protein to tyrosine. Homozygosity for the C282Y variant is associated with 60-90% of all cases of HH. Additionally, 3-8% of individuals affected with HH are heterozygous for this variant. Penetrance for elevated serum iron indices among C282Y homozygotes is variable. However, the penetrance for the characteristic clinical end points (end organ damage) is quite low. There is no test that can predict whether an individual with a C282Y homozygote will develop clinical symptoms. A specific PCSK7 variant, which is associated with iron metabolism, has been investigated as a possible predictor of cirrhosis risk in HH patients homozygous for the HFE C282Y variant.

Another significant HFE variant is referred to as H63D which changes histidine at position 63 to aspartic acid. Homozygosity for H63D is insufficient to cause clinically significant iron overload in the absence of modifying factors. However, compound 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.

The clinical significance of a third HFE variant, S65C (serine at position 65 changed to cysteine), 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 variants in HFE and in non-HFE genes (eg, transferrin receptor 2, TFR2) resulting in iron overload syndromes are rare.

With the advent of genetic testing in the late 1990s, HFE-related HH is now frequently identified in asymptomatic probands and in asymptomatic relatives of patients who are known to have the disease. 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 recognition of the different stages and progression of hemochromatosis. These stages were defined as:
1) Stage 1: those patients with “genetic susceptibility” who have the genetic disorder but with no increase in iron stores.
2) Stage 2: those patients with the genetic disorder who have phenotypic evidence of iron overload but no tissue or end organ damage.
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3) Stage 3: those individuals who have the genetic disorder with iron overload and iron deposition to the degree that tissue and end organ damage occurs.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for genetic testing for hemochromatosis when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Hemochromatosis is covered

Genetic testing for HFE gene variants may be considered medically necessary in a patient with abnormal serum iron indices indicating iron overload.

Genetic testing for HFE gene variants may be considered medically necessary in individuals with a family history of hemochromatosis in a first degree relative.

When Genetic Testing for Hemochromatosis is not covered

Genetic testing for hereditary hemochromatosis in screening of the general population is considered investigational.

Policy Guidelines

The evidence for genetic testing for hereditary hemochromatosis in individuals who have abnormal iron indices, clinical signs of iron overload, or are first degree relatives of persons with hereditary hemochromatosis includes retrospective and prospective observational studies. Relevant outcomes include test accuracy, test validity, and changes in disease status. These studies have established high analytic validity of genetic testing. Studies have demonstrated that current genetic testing detects the large majority of HH disease, but that among those with positive tests (HH homozygotes), penetrance for clinical disease is low. There is no direct evidence of the clinical utility of genetic testing, but along with prior knowledge regarding the effectiveness of treatment for clinical iron overload, there is a strong chain of indirect evidence that supports definitive genetic diagnosis of persons with early signs of HH and of first degree relatives of persons with HH. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
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The evidence for genetic testing for hereditary hemochromatosis in asymptomatic individuals in the general population with no family history of hereditary hemochromatosis includes, in addition to the above studies of analytic and clinical validity, observational studies of screening in population samples. Relevant outcomes include test accuracy, test validity, and changes in disease status. These studies establish population prevalence of genetic HH, and serve as partial evidence to estimate penetrance of disease. Low prevalence of HH homozygosity in the general population and incomplete penetrance of clinical disease do not support a chain of evidence for clinical utility of genetic testing in an unscreened population. The evidence is insufficient to determine the effects of the technology on health outcomes.

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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81256

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Specialty Matched Consultant Advisory Panel review 1/2013


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Specialty Matched Consultant Advisory Panel review 1/2014


Specialty Matched Consultant Advisory Panel review 4/2015

Medical Director review 4/2015


Medical Director review 3/2016


Specialty Matched Consultant Advisory Panel review 3/2017

Medical Director review 3/2017


Medical Director review 5/2017

**Policy Implementation/Update Information**

6/29/12 New policy developed. Genetic testing for HFE gene mutations may be considered medically necessary in a patient with abnormal serum iron indices indicating iron overload. Genetic testing for HFE gene mutations may be considered medically necessary in individuals with a family history of hemochromatosis in a first degree relative. Genetic testing for hereditary hemochromatosis in screening of the general population is considered investigational. Medical Director review 6/2012. Policy noticed on 6/29/12 for effective date of 10/01/12. (mco)

2/12/13 Specialty Matched Consultant Advisory Panel review 1/2013. No changes to Policy Statements. (mco)


5/27/14 References updated. Description section updated. No changes to Policy Statements. (mco)


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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.