Corporate Medical Policy

Genetic Testing for Hereditary Hemochromatosis AHS – M2012

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Description of Procedure or Service

Definitions
Hereditary hemochromatosis (HH) is a genetic disease which causes excessive absorption of dietary iron and storage particularly in the skin, heart, liver, pancreas, and joints due to mutations of genes involved in iron metabolism and homeostasis, including those encoding for HFE, hepcidin, hemouvelin, transferrin receptor, ferritin, ferroportin, and ceruloplasmin (Schrier & Bacon, 2017, 2018).

For policy regarding diagnostic testing of ferritin, transferrin, and hepcidin, please see policy titled, Diagnostic Testing of Iron Homeostasis & Metabolism.

Related Policies
Diagnostic Testing of Iron Homeostasis & Metabolism AHS – G2011

***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 hereditary hemochromatosis when it is determined the medical criteria or reimbursement guidelines 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 Hereditary Hemochromatosis is covered

1. HFE genotyping (to confirm the presence of mutation in C282Y, H63D, or S65C) is considered medically necessary for:
   A. Individuals with either serum transferrin saturation >45% or elevated serum ferritin levels; OR
   B. Individuals with a first degree relative with confirmed HH
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When Genetic Testing for Hereditary Hemochromatosis is not covered

General population screening for HH via genetic testing is considered investigational.

Policy Guidelines

Scientific Background
Iron homeostasis is a complex process where the small peptide hormone hepcidin plays a major role by binding the sole mammalian iron exporter, ferroportin (FPN1), leading to FPN1 degradation by lysosomes. Hepcidin production is sensitive to extracellular iron concentrations by way of HFE and the transferrin receptors (TfR). The HFE protein has been shown to interact with both TfR1 and TfR2, initiating the BMP-SMAD signaling pathway upon transferrin binding. This signaling cascade ultimately increases expression of the HAMP gene that encodes for hepcidin (Pietrangelo, 2015; Vujić, 2014).

Hereditary hemochromatosis (HH) is an iron-storage disease caused by genetic mutations, most often in the HFE gene, resulting in chronic hyperabsorption of dietary iron and iron accumulation primarily in the liver, pancreas, and heart, which can potentially result in impaired organ structure and function. This can ultimately result in liver cirrhosis, liver cancer, diabetes, congestive heart failure and osteoarthritis, as well as other serious conditions. Non-HFE hemochromatosis includes genetic mutations to hepcidin, ferroportin, ferritin, transferrin receptor 2, and ceruloplasmin. Left untreated, iron overload can result in death (Fleming, & Ponka, 2012; Schrier & Bacon, 2017. 2018).

Three-point mutations in HFE have been identified in HH: C282Y, H63D, and S65C. Homozygous C282Y mutation, according to one study in the U.S., was present in 83% of HH cases (Feder et al., 1996; Schrier & Bacon, 2017). C282Y HFE mutations are relatively common, especially in Caucasians of northern European origin, particularly Nordic or Celtic ancestry, with homozygosity among Caucasians being 1:200-300. The frequency of the C282Y allele ranges from as high as 12.5% in Ireland to 0% in southern Europe (Pietrangelo, 2015). This mutation disrupts disulfide bridge formation, preventing association with TfR1 (Vujić, 2014). The H63D mutation stabilizes the HFE-TfR1 complex and has a higher prevalence with a mean allele frequency of approximately 14%; however, phenotypically, H63D homozygosity rarely leads to HH (Pietrangelo, 2015; Vujić, 2014). A recent study by Joly and colleagues show a link between the H63D mutation and patients having severe complications from alpha 1-antitrypsin deficiency (1ATD). 1ATD patients who also have the H63D HFE mutation have an increased risk of “developing significant chronic hepatic injuries (hepatomegaly, chronic cholestasis, elevated liver enzymes) and at risk developing liver cirrhosis (Joly et al., 2017).” An earlier study reported that 7.8% of HH chromosomes containing neither the C282Y nor H63D mutations had the S65C mutation, suggesting that it is associated with a more mild form of HH (Mura, Raguenes, & Ferec, 1999). Moreover, HFE gene variants are found more frequently in patients suffering from idiopathic pulmonary fibrosis (IPF). “The frequency of C282Y, S65C and H63D HFE allelic variants was markedly higher in IPF compared with controls (40.4% versus 22.4%, OR 2.35, p=0.008) and was associated with higher iron-dependent oxygen radical generation…[suggesting] iron dysregulation associated with HFE allelic variants may play an important role in increasing susceptibility to environmental exposures, leading to recurring injury and fibrosis in IPF (Sangiuolo et al., 2015).”

Juvenile hemochromatosis (JH) or type II hemochromatosis is caused by mutations in the gene encoding the protein hemojuvelin. This recessive, rare form of hemochromatosis is suspected of inhibiting hepcidin production by a decrease in the bone morphogenetic protein signaling pathway (Schrier & Bacon, 2017). Unlike classical HH, JH typically develops before the age of 30, progresses at a greater rate, and is associated with iron overload, leading to severe clinical complications. An Italian study has identified at least 17 different mutations that can cause JH (Lanzara et al., 2004). A second form of JH (type IIB), also autosomal recessive, is caused by
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mutations to the HAMP gene that encodes for hepcidin (Radford-Smith, Powell, & Powell, 2018). This form also typically presents before the age of 30 with both hepatic and extrahepatic symptoms, including hypogonadism, cardiac abnormalities, and endocrine dysfunctions; however, with early treatment, symptoms can improve and iron levels can normalize (Fonseca et al., 2016; Lescano, Tavares, & Santos, 2017).

Mutations in the transferrin receptor 2 gene are rare; however, either homozygosity or compound heterozygosity can result in phenotypic hemochromatosis (Schrier & Bacon, 2017). Typically, the first biochemical abnormality is evident when the patient is in their 20s or 30s when TSAT elevation occurs. This form of hemochromatosis can result in liver disease due to hepatocellular iron accumulation and fibrosis (Pietrangelo, 2004). This form of hemochromatosis can result in variability in severity, “depending on the phenotypic impact of the mutation” (Bardou-Jacquet et al., 2013).

Mutations in the iron exporter ferroportin, FPN1, encoded by the gene SLC40A1 (classified as SLC11A3 in older literature), can result in an autosomal dominant form of HH. They type of ferroportin disease is dictated by the nature of the mutation—loss of function mutations, classical ferroportin disease, result in excess iron accumulation in macrophages, ferritinemia, and mild anemia whereas gain of function mutations, or non-classical ferroportin disease, result in hepcidin-resistant ferroportin, leading to iron accumulation in the hepatic parenchyma (Schrier & Bacon, 2017). Typically, the earliest biochemical abnormalities can begin to appear within the first decade of life, but the clinical onset of liver disease may not appear until adulthood (patients in their 40s). Unlike HFE-derived HH, ferroportin diseases, although rare, are pan-ethnic (Pietrangelo, 2004; Zhang, Lv, Huang, & Ou, 2017).

The standard of care for all forms of HH is reduction of iron via therapeutic, life-long phlebotomy with early initiation of treatment. Iron chelation and modifications to diet such as avoidance of iron, discontinuance of iron-containing supplements, and avoidance of alcohol can also be recommended. Monitoring of serum ferritin and TSAT are required to manage treatment and assess disease progression. “Improvements in overall wellbeing, including fatigue, liver function (pre-cirrhosis) and skin pigmentation, are most noticeable. On the other hand, if cirrhosis is already well established, it is generally considered irreversible (Radford-Smith et al., 2018).”

Clinical Validity and Utility

“HFE gene testing can be used to diagnose hemochromatosis in symptomatic patients, but analyses of liver histology and full gene sequencing are required to identify patients with rare, non-HFE forms of the disease. Due to the central pathogenic role of hepcidin, it is anticipated that nongenetic causes of hepcidin loss (eg, end-stage liver disease) can cause acquired forms of hemochromatosis (Pietrangelo, 2015).”

A study by Bulaj and colleagues published in the New England Journal of Medicine found that of the 10% of Caucasians heterozygous for classical HH, 20% of males and 8% of females had higher than normal mean serum ferritin concentrations than the control group and that 4% of males and 8% of females had elevated TSAT levels as compared to the control, wildtype group. “The clinical and biochemical expression of hemochromatosis was more marked in heterozygotes with paternally transmitted mutations than in those with maternally transmitted mutations. Liver-biopsy abnormalities were generally associated with alcohol abuse, hepatitis, or porphyria cutanea tarda. The phenotype of persons heterozygous for hemochromatosis differs from that of normal subjects, but complications due to iron overload alone in these heterozygotes are extremely rare (Bulaj, Griffen, Jorde, Edwards, & Kushner, 1996).”

A comprehensive German study in the technical performance and clinical relevance of HFE C282Y testing found that 1.7% of the patients tested for this specific point mutation were homozygous for C282Y; although, it should be noted that 42.6% of these patients had already
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been clinically diagnosed with hemochromatosis. Regarding the technical performance of the genetic test, it had an accuracy of 99.6% with an overall error rate of 0.24%. “The analytic specificity of the tests methods with respect to the detection of homozygosity for C282Y was 100% (7726 of 7726 nonhomozygous 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%). We conclude that the test methods for C282Y are robust, highly sensitive and specific, and that a DNA-based HH-screening program can be performed at reasonable laboratory costs (Stuhrmann, Strassburg, & Schmidtke, 2005).”

Another systematic review in 2008 of eleven different studies for classical HH testing in at-risk populations show that the “clinical sensitivity of C282Y homozygosity for hereditary haemochromatosis ranged from 28.4% to 100%; when considering studies that used strict criteria to classify hereditary haemochromatosis clinical sensitivity ranged from 91.3% to 92.4% (Bryant et al., 2008).” Another study investigating the accuracy of self-reporting family history of hemochromatosis show that 81.4% of patients reporting a family history for hemochromatosis correlated positively. The authors then conclude: “Self-reported family history of hemochromatosis or iron overload can be used to identify individuals whose risk of hemochromatosis or iron overload and associated conditions is increased. These individuals could benefit from further evaluation with iron phenotyping and HFE mutation analysis (Acton et al., 2008).”

Applicable Federal Regulations

Recently, Food and Drug Administration has authorized direct-to-consumer Genetic Health Risk Hereditary Hemochromatosis test developed by 23andMe. This test provides information on an individual’s genetic predisposition from European descent for Hereditary Hemochromatosis by testing 2 variants (C282Y; H63D) in the HFE gene in genomic DNA obtained from a human saliva. However, this test cannot determine an individual’s overall risk of developing a disease (AACC, 2017; FDA 2017).

Additionally, many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Guidelines and Recommendations

United States Preventive Services Task Force (USPSTF)

The United States Preventive Services Task Force (USPSTF) recommends against genetic screening for HH in the general, asymptomatic population, due to the low penetrance of the disease among those with causative mutations (USPSTF, 2014; Whitlock, Garlitz, Harris, Beil, & Smith, 2006). This 2006 guidelines is now listed as an “Inactive Topic” as of 9/17/2018. The state the following:

“The U.S. Preventive Services Task Force (USPSTF) has decided not to review the evidence and update its recommendations for this topic. The previous evidence review and recommendation may contain information that is outdated.

The USPSTF bases its recommendations on current evidence about preventive services. The USPSTF decides not to update some topics (or “inactivate” them) for a number of reasons. Topics may be inactivated because they are no longer relevant to clinical practice. This may be the result of changes in technology, a new understanding of the etiology or natural history of the disease, or the evolving natural history of the disease. Topics may also be inactivated because
they involve services that cannot be implemented in a primary care setting or are not referable by a primary care clinician. In addition, topics that have a low public health burden or that otherwise fall outside the scope of the USPSTF may be inactivated.

The USPSTF encourages primary care clinicians to consult other sources for current evidence regarding this topic. If new evidence becomes available, the USPSTF may elect to update this topic (USPSTF, 2018).

**Centers for Disease Control and Prevention**

The Centers for Disease Control and Prevention also do not recommend screening for HFE mutations in the general population. (Wetterhall, Cogswell, & Kowdley, 1998).

**American Association for the Study of Liver Diseases (AASLD) (Bacon, Adams, Kowdley, Powell, & Tavill, 2011)**

American Association for the Study of Liver Diseases (AASLD) Recommendations:

1. We recommend that patients with abnormal iron studies should be evaluated as patients with hemochromatosis, even in the absence of symptoms. (A)
2. All patients with evidence of liver disease should be evaluated for hemochromatosis. (1B)
3. In a patient with suggestive symptoms, physical findings, or family history, a combination of 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)
4. Diagnostic strategies using serum iron markers should target high-risk groups such as those with a family history of HH or those with suspected organ involvement. (1B)
5. 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. (1A)

**European Molecular Quality Network (Porto et al., 2016)**

Recommendations for diagnostic and predictive testing:

1. Population screening for the p.C282Y variant is not currently recommended (1B).
2. It is considered to be good practice to confirm elevated TS before HFE genetic diagnosis testing (1B).
3. Testing adult siblings (brothers and sisters) of p.C282Y homozygotes is recommended owing to the increased risk of p.C282Y homozygosity and related increased morbidity (1B).
4. Testing adult offspring of p.C282Y homozygotes is recommended owing to increased risk of p.C282Y homozygosity and related increased morbidity (1B).
5. Testing asymptomatic parents of p.C282Y homozygotes is not recommended systematically but rather as a clinical decision depending on their age, sex and ferritin, all three influencing the probability to develop severe iron overload (1C).
7. HFE testing of minors is not recommended (1B).
8. Prenatal diagnosis is not appropriate in HFE-related HH because it is a treatable, adult onset condition (1C).
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Hereditary hemochromatosis is one of the most common causes of inherited liver disorders which causes abnormal liver chemistries. In the cases where patients have abnormal liver chemistries without acute hepatitis, ACG recommends (“strong recommendation, very low level of evidence”) that those patients should undergo testing for hereditary hemochromatosis with an iron level, transferrin saturation, and serum ferritin. “HFE gene mutation analysis should be performed in patients with transferrin saturation >45% and/or elevated serum ferritin.”

American College of Medical Genetics and Genomics (ACMG, 2015)

ACMG has listed HFE genetic testing on its Choosing Wisely list. They recommend against ordering HFE genetic test for a patient without iron overload or a family history of HFE-associated HH.

British Society for Haematology (BSH) (Fitzsimons, Cullis, Thomas, Tsochatzis, & Griffiths, 2018)

The BSH recommendations include the following…

1. Unselected population screening for HFE gene mutation is not recommended. (1B)
2. Genetic haemochromatosis (GH) patients who present with serum ferritin (SF) >1000 µg/l and any with raised transaminases should be referred to a hepatologist for fibrosis assessment and exclusion of cirrhosis. (1B)
3. Patients of north European ancestry with clinical features suggestive of GH should have the following laboratory investigations; full blood count (FBC), liver function tests (LFTs), SF and transferrin saturation (Tsat). Molecular testing for HFE GH should follow if results fulfil the criteria of recommendation 5 (see below). (1B)
4. All adult patients of north European ancestry with unexplained raised SF and random Tsat (>300 µg/l and >50% males; >200 µg/l and >40% females) and normal FBC should have molecular testing for HFE GH. (1B)
5. Laboratory screening to include FBC, LFTs, SF, Tsat and HFE should be offered to family members after the diagnosis of HFE GH. Family screening should include parents (if available), siblings, partner and children (over the age of consent). Extended family screening is not recommended if an individual is identified as a C282Y/H63D compound heterozygote. (1B)
6. Investigation of all confirmed C282Y homozygotes should include FBC, LFTs, SF and Tsat. Thereafter further investigation may be required as follows:
   i. SF <1000 µg/l, normal LFTs, normal clinical examination; no further investigation required. Follow recommendation [7]. (1C)
   ii. SF >1000 µg/l and or abnormal LFTs. All such patients require referral to Hepatology for fibrosis assessment to exclude the presence of cirrhosis. A minimum would be elastography. For patients with confirmed cirrhosis monitor with -fetoprotein (AFP) and hepatic ultrasound every 6 months. (2C)
7. Non C282Y homozygotes with significant iron loading as confirmed by magnetic resonance imaging and or liver biopsy should be investigated for rare iron loading genotypes or digenic inheritance. (1C)
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8. At diagnosis, all fit GH patients with biochemical iron loading should undergo weekly venesection until SF ~ 20–30 µg/l and Tsat <50%. During this phase of venesection FBC should be monitored weekly and SF Tsat monitored monthly. Homozygotes with normal iron indices and compound heterozygotes with minimal elevation of iron indices may be suitable for blood donation and annual monitoring of SF and Tsat. (1B)

9. During maintenance, venesect as required, preferably at a blood donation centre to maintain normal FBC, SF <50 µg/l and Tsat <50%. (1C)

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


FDA. (2017, 05/02/2017). EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR The 23andMe Personal Genome Service (PGS) Genetic Health Risk Test for Hereditary Thrombophilia, Alpha-1 Antitrypsin Deficiency, Alzheimer's Disease, Parkinson's Disease, Gaucher Disease Type 1, Factor XI Deficiency, Celiac Disease, G6PD Deficiency, Hereditary Hemochromatosis and Early-Onset Primary Dystonia DECISION SUMMARY Retrieved from https://www.accessdata.fda.gov/cdrh_docs/reviews/den160026.pdf


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Policy Implementation/Update Information

1/1/2019   BCBSNC will provide coverage for hereditary hemochromatosis is when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

For policy titled: Genetic Testing for Hereditary Hemochromatosis


10/29/19   Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed.
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2/11/20  Annual review by Avalon 4th Quarter 2019 CAB. No revisions and no change to policy intent. Medical Director review 12/2019. (jd)


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