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Corporate Medical Policy

Genetic Testing for Hereditary Hemochromatosis AHS – M2012

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Description of Procedure or Service

Description
Hereditary hemochromatosis (HH) is a genetic disease that causes excessive absorption of dietary iron and storage in the skin, heart, liver, pancreas, and joints due to mutations of genes involved in iron metabolism and homeostasis. The genes include the HFE gene, and those encoding for hepcidin, hemojuvelin, transferrin receptor, ferritin, ferroportin, and ceruloplasmin (Bacon, 2019; Bacon & Camaschella, 2020).

For policy regarding diagnostic testing of ferritin, transferrin, and hepcidin, please see policy titled, Diagnostic Testing of Iron Homeostasis & Metabolism AHS – G2011.

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

2. Panel testing* (See Note 1) for additional HH-related genes is considered medically necessary ONLY IF ALL of the following are met:

a. Testing for C282Y, H63D, and S65C mutation was negative AND
b. Patient presents with atypical symptoms of iron overload, such as endocrine or cardiac involvement AND
c. Other potential causes of elevated serum iron have been ruled out.

NOTE 1: For 5 or more genes being tested on the same platform, such as multi-gene panel next generation sequencing, please refer to Laboratory Procedures Reimbursement Policy AHS - R2162

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 transferrin receptors (TfR). The HFE protein has been shown to interact with both TfR1 and TfR2 and initiate 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. This may cause impaired organ structure and function, and can ultimately lead to liver cirrhosis, liver cancer, diabetes, cardiac hypertrophy, congestive heart failure, and osteoarthritis, as well as other serious conditions (Adris et al., 2019; Milman, Schioedt, Junker, & Magnussen, 2019). A diagnosis of *HFE*-associated HH is often times difficult without the presence of physical features (Adris et al., 2019). Non-*HFE* hemochromatosis, which accounts for about 20% of HH diagnoses, includes genetic mutations to hepcidin, ferroportin, ferritin, TfR2, and ceruloplasmin. If left untreated, iron overload can result in death (Bacon, 2019; Bacon & Camaschella, 2020; Fleming & Ponka, 2012; Santos et al., 2012).

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 (Bacon & Camaschella, 2020; Feder et al., 1996). C282Y *HFE* mutations are relatively common, especially in Caucasians of northern European origin, particularly Nordic or Celtic ancestry; homozygosity among Caucasians was reported at 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). The prevalence of HH Type 1 (HFE C282Y mutation) varies by ethnicity; "0.000039% in Asian individuals, 0.012% in black, 0.027 in Hispanic to 0.44% in non-Hispanic individuals with a peak of 1.2% in Ireland" (Piperno, Pelucchi, & Mariani, 2020). Despite the common nature of this mutation, only a proportion of these patients with the homozygous C282Y mutation will develop symptoms of HH (Piperno et al., 2020). 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 et al. (2017) identified a link between the H63D mutation and patients with 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 are at risk of developing liver cirrhosis (Joly et al., 2017). An earlier study reported that 7.8% of HH

genes, rather than containing neither the C282Y nor H63D mutations, actually 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 (*HJV/HFE2* causes Type IIA HH). This recessive, rare form of hemochromatosis is suspected of inhibiting hepcidin production by a decrease in the bone morphogenetic protein signaling pathway (Bacon & Camaschella, 2020). This condition is fully penetrant, but with varying degrees of onset depending on the mutation; *HFE2* HH can present in adult or older age instead of in juvenile years (Piperno et al., 2020). 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, such as liver damage, cardiomyopathy, and hypogonadotrophic hypogonadism (Santos et al., 2012). An Italian study identified at least 17 different mutations that can cause JH (Lanzara et al., 2004). Takami et al. (2020) discovered that JH develops "in females and males at a ratio of 3:2 with no age difference in the two groups." Earlier JH onset was also seen among patients with a L101P/L101P or R385X/R385X *HJV* gene mutation and later in those with I281T/I281T *HJV* gene mutations when compared to the most common G320V/G320V mutation (Takami et al., 2020).

A second form of JH (type IIB), also autosomal recessive, is caused by 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 (*TFR2*) gene are rare; however, either homozygosity or compound heterozygosity can result in a phenotypic Type 3 HH (Bacon & Camaschella, 2020; Santos et al., 2012). TfR2 is typically a sensor for iron levels in the body and is involved in hepcidin synthesis (Santos et al., 2012). Typically, the first biochemical abnormality is evident when transferrin saturation (TSAT) elevation occurs in the second or third decade of life; *TFR2* HH onset is normally earlier than *HFE* HH (De Gobbi & Roetto, 2018). This form of hemochromatosis can result in liver disease due to hepatocellular iron accumulation and fibrosis and can vary in severity "depending on the phenotypic impact of the mutation" (Bardou-Jacquet et al., 2013; Pietrangelo, 2004). This phenotype can include "abnormal liver function, diabetes, hypogonadism, cardiomyopathy and arthritis" (Santos et al., 2012).

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 (Moreno-Carralero et al., 2014; Politou et al., 2004). Ferroportin is normally responsible for iron transport across enterocytes and iron recycling by the reticuloendothelial system (Santos et al., 2012). This type of ferroportin disease is dictated by the nature of the mutation. For example, loss of function mutations, such as in classical ferroportin disease, result in excess iron accumulation in macrophages, ferritinemia, and mild anemia, whereas gain of function mutations, as seen in non-classical ferroportin disease or Type 4 HH, result in hepcidin-resistant ferroportin, leading to iron accumulation in the hepatic parenchyma (Bacon & Camaschella, 2020). These patients "hyperabsorb iron and present with high TSAT, high serum ferritin, ad tissue iron overload with evidence of toxic damage that may develop into adult age" (Piperno et al., 2020). 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).

Several proprietary gene panels are available for hereditary hemochromatosis, such as Invitae's panel (5 genes, *HAMP, HFE, HJV, SLC40A1, TFR2*) (Invitae, 2020) and Blueprint Genetics' panel (5 genes, *HAMP, HFE, HFE2, SLC40A1, TFR2*) (Blueprint, 2020). These panels often encompass the primary gene, *HFE*, as well as the rarer pathogenic variants that may also cause HH.

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 (Rombout-Sestrienkova et al., 2016). 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 pigmentations, are most noticeable. On the other hand, if cirrhosis is already well established, it is generally considered irreversible" (Radford-Smith et al., 2018).

Analytical Validity

Pietrangelo (2015) states that "*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 (e.g. end-stage liver disease) can cause acquired forms of hemochromatosis."

Specifically for the C282Y *HFE* mutation, Palomaki et al. (2003) found that the "analytic sensitivity for C282Y homozygosity is 98.4% (95% CI 95.9%–99.5%). The analytic specificity is 99.8% (99.4%–99.9%). At a frequency of 40 per 10,000 for the homozygous genotype, the analytic positive predictive value is 66%" after analyzing results from the Molecular Genetic Survey collected by the American College of Medical Genetics/College of American Pathologists between 1998 and 2002. The authors noted these results as a critical part of any confirmatory testing for identifying false-positive C282Y mutation test results in any potential population-based HH screening program.

A comprehensive German study researching 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 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 "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)."

The College of American Pathologists provided blinded proficiency testing (PT) for any interested laboratories completing common *HFE* genetic testing methods; researchers used 10 years of data provided from these PT studies to determine overall *HFE* testing laboratory performance. A total of 257 different labs participated and several different genotyping methods were used including "differential restriction enzyme fragment lengths (51%), melting curve-based methods (15%), probe-specific real-time PCR (TaqMan) methods (8%), direct sequencing (7%), and allele-specific PCR (7%)" (Press et al., 2016). A very low error rate was found (0.73% in 7,663 results), with more errors found in specific variants (C282Y heterozygous, H63D

homozygous, and C282Y homozygous); very high sensitivity and specificity values were identified at >98.5% and >99.5% respectively (Press et al., 2016).

Clinical Validity and Utility

A study by Bulaj, Griffen, Jorde, Edwards, and Kushner (1996) 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 et al., 1996).

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, the 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 showed that 81.4% of patients reporting a family history for hemochromatosis correlated positively. The authors then concluded: "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).

Lanktree et al. (2017) utilized next-generation sequencing (NGS) of an iron metabolism gene panel to provide patients with a non-*HFE* hemochromatosis diagnosis; the panel was constructed of 15 genes related to iron metabolism. A total of 190 patients with a potential iron overload were screened, and six were diagnosed with non-*HFE* iron overload based on homozygous hemojuvelin (*HFE2*) mutations (Lanktree et al., 2017). Additional pathogenic mutations were found from molecular sequencing results.

Rabideau, White, Anderson, and Deucher (2014) also used NGS in a panel with *HFE, HAMP, HFE2, SLC40A1,* and *TFR2* genes to detect rare, other HH-causing mutations not typically assayed. They found that these particular genes "resulted in an additional diagnostic yield compared to *HFE* C282Y and H63D testing alone," and that in patients with such a genetic attribution, management of care "can be personalized based on genotype-phenotype correlation (e.g. N144Y *SLC40A1* mutations may lead to reduced phlebotomy tolerance) and at-risk family members can be screened" (Rabideau et al., 2014).

A 2018 study by Sandhu et al. (2018) conducted a phenotypic analysis across both *HFE* and non-*HFE* variants of hemochromatosis to identify differences in severity of iron overload and disease presentation. Data from 156 patients with genetically confirmed autosomal recessive non-*HFE* HH were compared against 984 patients with *HFE*-p.C282Y homozygous HH, and were found to have both "an earlier age of onset and a more severe clinical course than *HFE* HH, with the most severe presentations found among those with *HJV* and *HAMP* HH (Sandhu et al., 2018). These two juvenile forms had a greater association with all clinical outcomes as well, including cardiomyopathy and hypogonadism, but not arthritis and arthropathy, which was found more in the *HFE* HH population. Higher proportions of those with non-*HFE* HH were derived from Italy (30%) and Greece (10%), and most of those with non-*HFE* HH were homozygous for their respective mutations. This study conveys how the type of HH mutation would influence the level of urgency for treatment of a patient's presentation (Sandhu et al., 2018).

HFE gene mutations, specifically C282Y and H63D, have also been tested in association with cancer. From a meta-analysis performed by Lv et al. (2016), "C282Y was found to increase the risk of cancer twofold in the recessive model and 1.1-fold in the allele mode… The results suggest that the C282Y/C282Y genotype is associated with a twofold elevated risk for breast cancer, a 1.7-fold elevated risk of colorectal, and a 3.6-fold increased risk of hepatocellular cancer." This study demonstrated the utility of *HFE* gene mutations beyond HH to cancer risk, and how "living environment, genetic background and dietary habits are candidate factors that influence the risk of cancer because of HFE mutations" (Lv et al., 2016).

HH, with mutations in the *HFE* gene, has been associated with osteoarthritis (Milman et al., 2019). A recent prospective cross-sectional study analyzed data from 940 patients younger than 70 years old previously diagnosed with end-stage osteoarthritis of the hip; all participants were compared to a healthy control of similar age and sex (Oppl et al., 2018). Results did not show a relationship between *HFE* mutations and osteoarthritis; the authors stated that "No greater prevalence of C282Y homozygosity mutation or elevated serum ferritin or transferrin saturation levels was found in the study cohort with severe osteoarthritis of the hip than in controls from the general population" (Oppl et al., 2018).

HH patients with *HFE* mutations typically present with elevated erythrocyte levels; until recently, this data has not been used in clinical practice. Adris et al. (2019) analyzed data from a total of 2,688 participants (144 with HH, 1844 healthy controls, and 700 with chronic diseases). Results showed that the "mean cell volume (MCV) and mean cell haemoglobin (MCH) were always significantly higher" in HH subjects when compared to other participants; thus, the use of erythrocyte parameters "demonstrated excellent diagnostic utility for detection of HH in men and women (AUROC 0.83-0.9; maximal sensitivity and specificity 82% and 78%)" (Adris et al., 2019).

Guidelines and Recommendations

United States Preventive Services Task Force (USPSTF) (USPSTF, 2014, 2018; Whitlock, Garlitz, Harris, Beil, & Smith, 2006)

The 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 et al., 2006). This 2006 guideline is now listed as an "Inactive Topic" as of 09/17/2018. USPSTF (2018) guidelines 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)."

Canadian Association for the Study of the Liver (CASL) and Choosing Wisely Canada (CWC) Choosing Wisely Canada-Top Five List in Hepatology (Brahmania et al., 2019)

The CASL developed a list of the top five recommendations in hepatology based on data provided by the CWC. One of these recommendations mention *HFE* genotyping:

- "Don't order *HFE* genotyping based on serum ferritin values alone to diagnose hereditary hemochromatosis (Brahmania et al., 2019).

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

The AASLD has published the following recommendations in Bacon et al. (2011):

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 Association for the Study of the Liver (EASL, 2010)

The EASL published clinical practice guidelines for *HFE* hemochromatosis. In general and patient populations, EASL (2010) states:

- "General population:
  - Genetic screening for HFE-HC is not recommended, because disease penetrance is low and only in few C282Y homozygotes will iron overload progress (1B).
- Patient populations:
  - HFE testing should be considered in patients with unexplained chronic liver disease pre-selected for increased transferrin saturation (1C).
  - HFE testing could be considered in patients with:
    - Porphyria cutanea tarda (1B).
    - Well-defined chondrocalcinosis (2C).
    - Hepatocellular carcinoma (2C).
    - Type 1 diabetes (2C).
  - HFE testing is not recommended in patients with
    - Unexplained arthritis or arthralgia (1C)"
    - Type 2 diabetes (1B)."

With regards to family screening, the EASL states "Siblings of patients with HFE-related HC must undergo screening, since they have a 25% chance of being susceptible. Serum ferritin, and

transferrin saturation should be assessed. Ideally HFE mutation analysis should be encouraged after appropriate counseling with regard to the pros and cons of testing (mortgage, insurance issues)" (EASL, 2010).

In using genetic testing to diagnose HH, the EASL adds:

- "Patients from liver clinics should be screened for fasting transferrin saturation and serum ferritin (1C) and offered genetic HFE testing if transferrin saturation is increased (1B)
- Diagnosis of HFE hemochromatosis should not be based on C282Y homozygosity alone, but requires evidence of increased iron stores (1B).
- Genetic testing of 'other hemochromatosis genes' (*TFR2, SLC40A1, HAMP, HJV*) could be considered in patients with increased iron stores after exclusion of C282Y homozygosity if (i) iron excess has been proven by direct assessment, i.e. by MRI or liver biopsy, and (ii) other hepatic and haematological disorders have been ruled out (2C)."

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

The EMQN has published the following 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 (1C).
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).
6. Systematic testing of adult first-degree relatives of p.C282Y heterozygotes is not currently recommended, in the absence of evidence of benefit (2C).
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) (Porto et al., 2016)."

American College of Gastroenterology (ACG) Clinical Guideline: Evaluation of Abnormal Liver Chemistries (Kowdley, Brown, Ahn, & Sundaram, 2019; Kwo, Cohen, & Lim, 2017)

HH 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; further, "*HFE* gene mutation analysis should be performed in patients with transferrin saturation ≥45% and/or elevated serum ferritin" (Kwo et al., 2017).

In regards to family members, the ACG has stated that "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)" (Kowdley et al., 2019).

The ACG also recommends 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 testing negative for the C282Y and H63D alleles (conditional recommendation, very low quality of evidence)" (Kowdley et al., 2019).

Regarding non-*HFE* HH, the ACG writes that "Before pursuing testing for non-*HFE* hemochromatosis, alternative explanations for elevated serum iron tests should be excluded, because abnormal iron studies due to conditions such as AUD or NAFLD are far more common than non-*HFE* hemochromatosis. Contrarily, sequencing of non-*HFE* genes may be considered in atypical cases of iron overload, such as a younger patient presenting with endocrine or cardiac involvement." (Kowdley et al., 2019)

American College of Medical Genetics and Genomics (ACMG, 2015, 2016)

ACMG has listed *HFE* genetic testing on its Choosing Wisely list. The ACMG has stated that "*HFE* genotyping should only be performed among individuals with iron overload (e.g., elevated fasting transferrin saturation >45%) or a known family history of *HFE*-associated hereditary hemochromatosis" (ACMG, 2016).

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

The BSH recommendations include the following as published by Fitzsimons et al. (2018):

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)
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)"

Applicable Federal Regulations

Recently, the U.S. Food and Drug Administration (FDA) has authorized a 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).

LabCorp (2019) has developed a hereditary hemochromatosis test which utilizes PCR for DNA analysis; this testing method utilizes a whole blood or swab kit and analyzes the C282Y, H63D, and S65C mutations of the *HFE* gene. This test has not been approved by the FDA.
A search of the FDA database on 10/28/2020 using the term "hereditary hemochromatosis" yielded 0 results. 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.

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, 81479

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

AACC. (2017, 06/01/2017). 23andMe Continues Rebound With FDA OK for First DTC Genetic Risk Tests. *Clinical Laboratory News.* Retrieved from https://www.aacc.org/publications/cln/articles/2017/june/23andme-continues-rebound-with-fda-ok-for-first-dtc-genetic-risk-tests
ACMG. (2015, 09/15/2016). Don't order HFE genetic testing for a patient without iron overload or a family history of HFE-associated hereditary hemochromatosis. *Choosing Wisely List of Recommendations.* Retrieved from http://www.choosingwisely.org/clinician-lists/american-college-medical-genetics-genomics-hfe-genetic-testing/
ACMG. (2016). American College of Medical Genetics and Genomics. Retrieved from http://www.choosingwisely.org/clinician-lists/american-college-medical-genetics-genomics-hfe-genetic-testing/
Acton, R. T., Barton, J. C., Passmore, L. V., Adams, P. C., McLaren, G. D., Leiendecker-Foster, C., . . . McLaren, C. E. (2008). Accuracy of family history of hemochromatosis or iron overload:

the hemochromatosis and iron overload screening study. *Clin Gastroenterol Hepatol, 6*(8), 934-938. doi:10.1016/j.cgh.2008.04.003
Adris, N., Hazeldine, S., Bentley, P., Trinder, D., Chua, A. C. G., Powell, L. W., . . . Olynyk, J. K. (2019). Detection of HFE Haemochromatosis in the clinic and community using standard erythrocyte tests. *Blood Cells Mol Dis, 74*, 18-24. doi:10.1016/j.bcmd.2018.10.003
Bacon, B. R. (2019, July 22). Clinical manifestations and diagnosis of hereditary hemochromatosis. *Uptodate.com.* Retrieved from https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-hereditary-hemochromatosis
Bacon, B. R., Adams, P. C., Kowdley, K. V., Powell, L. W., & Tavill, A. S. (2011). Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology, 54*(1), 328-343. doi:10.1002/hep.24330
Bacon, B. R., & Camaschella, C. (2020, February 25). HFE and other hemochromatosis genes. *UpToDate.com.* Retrieved from https://www.uptodate.com/contents/hfe-and-other-hemochromatosis-genes
Bardou-Jacquet, E., Cunat, S., Beaumont-Epinette, M. P., Kannengiesser, C., Causse, X., Sauvion, S., . . . Jouanolle, A. M. (2013). Variable age of onset and clinical severity in transferrin receptor 2 related haemochromatosis: novel observations. *Br J Haematol, 162*(2), 278-281. doi:10.1111/bjh.12350
Blueprint. (2020). Hereditary Hemochromatosis Panel. Retrieved from https://blueprintgenetics.com/tests/panels/metabolic-disorders/hereditary-hemochromatosis-panel/
Brahmania, M., Renner, E. L., Coffin, C. S., Yoshida, E. M., Wong, P., Zeman, M., & Shah, H. (2019). Choosing Wisely Canada-Top Five List in Hepatology: Official Position Statement of the Canadian Association for the Study of the Liver (CASL) and Choosing Wisely Canada (CWC). *Ann Hepatol, 18*(1), 165-171. doi:10.5604/01.3001.0012.7908
Bryant, J., Cooper, K., Picot, J., Clegg, A., Roderick, P., Rosenberg, W., & Patch, C. (2008). A systematic review of the clinical validity and clinical utility of DNA testing for hereditary haemochromatosis type 1 in at-risk populations. *J Med Genet, 45*(8), 513-518. doi:10.1136/jmg.2007.055806
Bulaj, Z. J., Griffen, L. M., Jorde, L. B., Edwards, C. Q., & Kushner, J. P. (1996). Clinical and biochemical abnormalities in people heterozygous for hemochromatosis. *N Engl J Med, 335*(24), 1799-1805. doi:10.1056/nejm199612123352403
De Gobbi, M., & Roetto, A. (2018). TFR2-Related Hereditary Hemochromatosis. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. H. Bean, K. Stephens, & A. Amemiya (Eds.), *GeneReviews((R))*. Seattle (WA): University of Washington, Seattle
University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.
EASL. (2010). EASL clinical practice guidelines for HFE hemochromatosis. *J Hepatol, 53*(1), 3-22. doi:10.1016/j.jhep.2010.03.001
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
Feder, J. N., Gnirke, A., Thomas, W., Tsuchihashi, Z., Ruddy, D. A., Basava, A., . . . Wolff, R. K. (1996). A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet, 13*(4), 399-408. doi:10.1038/ng0896-399
Fitzsimons, E. J., Cullis, J. O., Thomas, D. W., Tsochatzis, E., & Griffiths, W. J. H. (2018). Diagnosis and therapy of genetic haemochromatosis (review and 2017 update). *Br J Haematol, 181*(3), 293-303. doi:10.1111/bjh.15164
Fleming, R. E., & Ponka, P. (2012). Iron overload in human disease. *N Engl J Med, 366*(4), 348-359. doi:10.1056/NEJMra1004967
Fonseca, P. F., Cancado, R. D., Uellendahl Lopes, M. M., Correia, E., Lescano, M. A., & Santos, P. C. (2016). HAMP Gene Mutation Associated with Juvenile Hemochromatosis in Brazilian Patients. *Acta Haematol, 135*(4), 228-231. doi:10.1159/000444119

Invitae. (2020). Invitae Hereditary Hemochromatosis Panel. Retrieved from https://www.invitae.com/en/physician/tests/05201/
Joly, P., Vignaud, H., Di Martino, J., Ruiz, M., Garin, R., Restier, L., . . . Bouchecareilh, M. (2017). ERAD defects and the HFE-H63D variant are associated with increased risk of liver damages in Alpha 1-Antitrypsin Deficiency. *PLoS One, 12*(6), e0179369. doi:10.1371/journal.pone.0179369
Kowdley, K. V., Brown, K. E., Ahn, J., & Sundaram, V. (2019). ACG Clinical Guideline: Hereditary Hemochromatosis. *Am J Gastroenterol, 114*(8), 1202-1218. doi:10.14309/ajg.0000000000000315
Kwo, P. Y., Cohen, S. M., & Lim, J. K. (2017). ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol, 112*(1), 18-35. doi:10.1038/ajg.2016.517
LabCorp. (2019). Hereditary Hemochromatosis, DNA Analysis. Retrieved from https://www.labcorp.com/test-menu/27711/hereditary-hemochromatosis-dna-analysis#
Lanktree, M. B., Sadikovic, B., Waye, J. S., Levstik, A., Lanktree, B. B., Yudin, J., . . . Adams, P. C. (2017). Clinical evaluation of a hemochromatosis next-generation sequencing gene panel. *Eur J Haematol, 98*(3), 228-234. doi:10.1111/ejh.12820
Lanzara, C., Roetto, A., Daraio, F., Rivard, S., Ficarella, R., Simard, H., . . . Camaschella, C. (2004). Spectrum of hemojuvelin gene mutations in 1q-linked juvenile hemochromatosis. *Blood, 103*(11), 4317-4321. doi:10.1182/blood-2004-01-0192
Lescano, M. A., Tavares, L. C., & Santos, P. (2017). Juvenile hemochromatosis: HAMP mutation and severe iron overload treated with phlebotomies and deferasirox. *World J Clin Cases, 5*(10), 381-383. doi:10.12998/wjcc.v5.i10.381
Lv, Y. F., Chang, X., Hua, R. X., Yan, G. N., Meng, G., Liao, X. Y., . . . Guo, Q. N. (2016). The risk of new-onset cancer associated with HFE C282Y and H63D mutations: evidence from 87,028 participants. *J Cell Mol Med, 20*(7), 1219-1233. doi:10.1111/jcmm.12764
Milman, N. T., Schioedt, F. V., Junker, A. E., & Magnussen, K. (2019). Diagnosis and Treatment of Genetic HFE-Hemochromatosis: The Danish Aspect. *Gastroenterology Res, 12*(5), 221-232. doi:10.14740/gr1206
Moreno-Carralero, M. I., Munoz-Munoz, J. A., Cuadrado-Grande, N., Lopez-Rodriguez, R., Jose Hernandez-Alfaro, M., del-Castillo-Rueda, A., . . . Moran-Jimenez, M. J. (2014). A novel mutation in the SLC40A1 gene associated with reduced iron export in vitro. *Am J Hematol, 89*(7), 689-694. doi:10.1002/ajh.23714
Mura, C., Raguenes, O., & Ferec, C. (1999). HFE mutations analysis in 711 hemochromatosis probands: evidence for S65C implication in mild form of hemochromatosis. *Blood, 93*(8), 2502-2505.
Oppl, B., Husar-Memmer, E., Pfefferkorn, S., Blank, M., Zenz, P., Gollob, E., . . . Datz, C. (2018). HFE hemochromatosis screening in patients with severe hip osteoarthritis: A prospective cross-sectional study. *PLoS One, 13*(11), e0207415. doi:10.1371/journal.pone.0207415
Palomaki, G. E., Haddow, J. E., Bradley, L. A., Richards, C. S., Stenzel, T. T., & Grody, W. W. (2003). Estimated analytic validity of HFE C282Y mutation testing in population screening: the potential value of confirmatory testing. *Genet Med, 5*(6), 440-443. doi:10.1097/01.gim.0000096500.66084.85
Pietrangelo, A. (2004). Non-HFE hemochromatosis. *Hepatology, 39*(1), 21-29. doi:10.1002/hep.20007
Pietrangelo, A. (2015). Genetics, Genetic Testing, and Management of Hemochromatosis: 15 Years Since Hepcidin. *Gastroenterology, 149*(5), 1240-1251.e1244. doi:10.1053/j.gastro.2015.06.045
Piperno, A., Pelucchi, S., & Mariani, R. (2020). Inherited iron overload disorders. *Transl Gastroenterol Hepatol, 5*, 25. doi:10.21037/tgh.2019.11.15
Politou, M., Kalotychou, V., Pissia, M., Rombos, Y., Sakellaropoulos, N., & Papanikolaou, G. (2004). The impact of the mutations of the HFE gene and of the SLC11A3 gene on iron overload in Greek thalassemia intermedia and beta(s)/beta(thal) anemia patients. *Haematologica, 89*(4), 490-492. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15075083
Porto, G., Brissot, P., Swinkels, D. W., Zoller, H., Kamarainen, O., Patton, S., . . . Keeney, S. (2016). EMQN best practice guidelines for the molecular genetic diagnosis of hereditary hemochromatosis (HH). *Eur J Hum Genet, 24*(4), 479-495. doi:10.1038/ejhg.2015.128

Press, R. D., Eickelberg, G., McDonald, T. J., Halley, J., Long, T., Tafe, L. J., & Weck, K. E. (2016). Highly accurate molecular genetic testing for HFE hereditary hemochromatosis: results from 10 years of blinded proficiency surveys by the College of American Pathologists. *Genet Med, 18*(12), 1206-1213. doi:10.1038/gim.2016.34
Rabideau, M. M., White, H. J., Anderson, M., & Deucher, A. (2014). Clinical Testing of Five Hereditary Hemochromatosis-Related Genes: Preliminary Evidence for the Benefit of Next Generation Sequencing. *Blood, 124*(21), 1355-1355. doi:10.1182/blood.V124.21.1355.1355
Radford-Smith, D. E., Powell, E. E., & Powell, L. W. (2018). Haemochromatosis: a clinical update for the practising physician. *Internal Medicine Journal $V 48*(5), 509-516.
Rombout-Sestrienkova, E., Winkens, B., Essers, B. A., Nieman, F. H., Noord, P. A., Janssen, M. C., . . . Koek, G. H. (2016). Erythrocytapheresis versus phlebotomy in the maintenance treatment of HFE hemochromatosis patients: results from a randomized crossover trial. *Transfusion, 56*(1), 261-270. doi:10.1111/trf.13328
Sandhu, K., Flintoff, K., Chatfield, M. D., Dixon, J. L., Ramm, L. E., Ramm, G. A., . . . Wallace, D. F. (2018). Phenotypic analysis of hemochromatosis subtypes reveals variations in severity of iron overload and clinical disease. *Blood, 132*(1), 101-110. doi:10.1182/blood-2018-02-830562
Sangiuolo, F., Puxeddu, E., Pezzuto, G., Cavalli, F., Longo, G., Comandini, A., . . . Saltini, C. (2015). HFE gene variants and iron-induced oxygen radical generation in idiopathic pulmonary fibrosis. *Eur Respir J, 45*(2), 483-490. doi:10.1183/09031936.00104814
Santos, P. C., Dinardo, C. L., Cançado, R. D., Schettert, I. T., Krieger, J. E., & Pereira, A. C. (2012). Non-HFE hemochromatosis. *Rev Bras Hematol Hemoter, 34*(4), 311-316. doi:10.5581/1516-8484.20120079
Stuhrmann, M., Strassburg, C., & Schmidtke, J. (2005). Genotype-based screening for hereditary haemochromatosis. I: Technical performance, costs and clinical relevance of a German pilot study. *Eur J Hum Genet, 13*(1), 69-78. doi:10.1038/sj.ejhg.5201287
Takami, A., Tatsumi, Y., Sakai, K., Toki, Y., Ikuta, K., Oohigashi, Y., . . . Takami, K. (2020). Juvenile Hemochromatosis: A Case Report and Review of the Literature. *Pharmaceuticals (Basel), 13*(8). doi:10.3390/ph13080195
USPSTF. (2014, 06/2014). Guide to Clinical Preventive Services. Retrieved from https://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/guide/section2b.html#hemo
USPSTF. (2018, 09/2018). Hemochromatosis: Screening. *Inactive Topic.* Retrieved from https://www.uspreventiveservicestaskforce.org/BrowseRec/InactiveTopic/219
Vujić, M. (2014). Molecular basis of HFE-hemochromatosis. *Front Pharmacol, 5*. doi:10.3389/fphar.2014.00042
Whitlock, E. P., Garlitz, B. A., Harris, E. L., Beil, T. L., & Smith, P. R. (2006). Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med, 145*(3), 209-223.
Zhang, W., Lv, T., Huang, J., & Ou, X. (2017). Type 4B hereditary hemochromatosis associated with a novel mutation in the SLC40A1 gene: A case report and a review of the literature. *Medicine (Baltimore), 96*(38), e8064. doi:10.1097/md.0000000000008064

Specialty Matched Consultant Advisory Panel review 3/2020

Medical Director review 3/2020

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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

4/16/2019 Title change updated throughout policy. Updated definitions and added related policies section for "Diagnostic Testing of Iron Homeostasis & Metabolism AHS – G2011". Removed item 1 concerning serum ferritin testing and TSAT from When Covered section. Updated policy guidelines and reference section. Removed 83540, 83550, and 82728 from Billing/Coding section. Medical Director review 4/2019. (jd)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed.

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)

3/31/20 Specialty Matched Consultant Advisory Panel review 3/2020. Medical Director review 3/2020. (jd)

2/9/21 Annual review by Avalon 4th Quarter 2020 CAB. Description section updated. Added item #2 a-c and "NOTE 1" to the When Covered section. Policy guidelines updated. Added CPT code 81479 to the Billing/Coding section. References updated. Medical Director review 1/2021. (jd)

3/31/21 Specialty Matched Consultant Advisory Panel review 3/2021. Medical Director review 3/2021. (jd)