Sentara Health Plans

Genetic Testing for Hereditary Hemochromatosis

Policy Number: AHS – M2012 – Genetic Testing for Hereditary Hemochromatosis	Prior Policy Name and Number, as applicable: • M2012 – Hereditary Hemochromatosis
Initial Policy Effective Date: 12/01/2024	

I. Policy 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 & Camaschella, 2021; Bacon & Phatak, 2023).

For policy regarding diagnostic testing of ferritin, transferrin, and hepcidin, please see AHS-G2011.

Terms such as male and female are used when necessary to refer to sex assigned at birth.

II. Related Policies

Policy Number	Policy Title
AHS-G2011	Diagnostic Testing of Iron Homeostasis & Metabolism

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) For individuals with serum transferrin saturation ≥45% or elevated serum ferritin (see Note 1) **or** who have a first-degree relative (see Note 2) with confirmed hereditary hemochromatosis (HH), *homeostatic iron regulator* (*HFE)* mutation genotyping (C282Y, H63D, or S65C) **MEETS COVERAGE CRITERIA**.

2) Multi-gene panel testing (see Note 3) for additional HH-related genes **MEETS COVERAGE CRITERIA** only when **all** of the following conditions are met:

a) Individual has tested negative for common mutations in *HFE* (C282Y, H63D, and S65C);

b) Individual presents with atypical symptoms of iron overload, such as endocrine or cardiac involvement;

c) All other potential causes of elevated serum iron have been ruled out.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

3) For the general population, screening for HH via genetic testing **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note 1: Elevated serum ferritin is defined as >300 ng/mL in males or postmenopausal females; >200 ng/mL in premenopausal females (Bacon & Phatak, 2023).

Note 2: First-degree relatives include parents, full siblings, and children of the individual.

Note 3: For 5 or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

IV. Table of Terminology

Term	Definition
1ATD	Alpha 1-antitrypsin deficiency
AASLD	American Association for the Study of Liver Diseases
AUD	Alcohol use disorder
ACG	American College of Gastroenterology
BSH	British Society for Haematology
CASL	Canadian Association for the Study of the Liver
CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CWC	Choosing Wisely Canada
DNA	Deoxyribonucleic acid
EASL	European Association for the Study of the Liver
FBC	Full blood count
FPN1	Ferroportin
GH	Genetic hemochromatosis
HAMP	*Hepcidin antimicrobial peptide*
HC	Hemochromatosis
HFE	*Homeostatic iron regulator*
HJV	Hemojuvelin
HH	Hereditary hemochromatosis
IPF	Idiopathic pulmonary fibrosis
LDTs	Laboratory-developed tests

LFT	Liver function test
NAFLD	Nonalcoholic fatty liver disease
NGS	Next-generation sequencing
PCR	Polymerase chain reaction
SF	Serum ferritin
SLC11A3	Previous gene name of *SLC40A1*
SLC40A1	*Solute carrier family 40 member 1 gene*
TfR/TFR	Transferrin receptor
Tsat	Transferrin saturation
USPSTF	U.S. Preventive Services Task Force

V. 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 et al., 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 & Camaschella, 2021; Bacon & Phatak, 2023; 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, 2021; 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 one (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 et al., 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 et al., 1999). Moreover, *HFE* gene variants are found more frequently in patients suffering from idiopathic pulmonary fibrosis (IPF), such that "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, 2021). 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 et al., 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 et al., 2017).

Mutations in the transferrin receptor two (*TFR2*) gene are rare; however, either homozygosity or compound heterozygosity can result in a phenotypic Type three HH (Bacon & Camaschella, 2021; 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 four HH, result in hepcidin-resistant ferroportin, leading to iron accumulation in the hepatic parenchyma (Bacon & Camaschella, 2021). 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 et al., 2017).

Proprietary Testing

Several proprietary gene panels are available for hereditary hemochromatosis, such as Invitae's panel (five genes, *HAMP, HFE, HJV, SLC40A1, TFR2*) (Invitae, 2023) and Blueprint Genetics' panel (five genes, *HAMP, HFE, HFE2, SLC40A1, TFR2*) (Blueprint, 2022). 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 where "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 et al., 2005).

The College of American Pathologists provided blinded proficiency testing (PT) for any interested laboratories completing common *HFE* genetic testing methods; researchers used ten 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 (eight percent), direct sequencing (seven percent), and allele-specific PCR (seven percent)" (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 Utility and Validity

A study by Bulaj et al. (1996) published in the New England Journal of Medicine found that of the ten percent of Caucasians heterozygous for classical HH, 20% of males and eight percent of females had higher than normal mean serum ferritin concentrations than the control group and that four percent of males and eight percent 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 et al. (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 (ten percent), 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).

The *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).

The finding with hepatocellular cancer was conferred by Atkins et al. (2020), who, in a cohort of 451,186 UK Biobank participants who had the HFE p.282Y and p.H63D phenotypes, found that among 1294 male p.282Y homozygotes, there were 21 incident hepatic malignancies. A significant finding was not found to be statistically significant in women. For projections of the male p.282Y homozygote lifetime risk of primary hepatic malignancy up to age 75, the risk was "7.2% (95% CI, 3.9%-13.1%), compared with 0.6% (95% CI, 0.4%-0.7%) for men with neither variant, and the risk of death was 19.5% (95% CI, 15.8%-24.0%), compared with 15.1% (95% CI, 14.7%-15.5%) among men with neither variant" (Atkins et al., 2020).

Moreover, Lim et al. (2020) performed a retrospective analysis on individuals in Newfoundland and Labrador, Canada, homozygous for the C282Y mutation between 1999 and 2009. Of the 306 individuals with C282Y/C282Y and with adequate follow-up, 56 (18.3%) were observed to have end-organ damage, with 5.8% developing liver disease and that such end organ damage was observed more frequently in men (24.3%) than in women (10.5%); however, when separated across pre- vs post-menopausal groups for women, iron overload-related disease was met by 4.1% and 18.3%, respectively. As such, the authors concluded that given the relatively low

clinical penetrance of HH mutations, C282Y homozygosity uncommonly causes end-organ damage and liver disease (Lim et al., 2020).

Hereditary hemochromatosis, 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).

Tamosauskaite et al. (2019) also conducted a study on musculoskeletal effects of HH C282 homozygosity among 200,975 UK Biobank participants aged 60-70 years. They tested the association with Fried frailty, sarcopenia, and chronic pain, and found that "C282Y homozygote men had increased likelihood of reporting chronic pain (odds ratio [OR] 1.23: 95% confidence interval [CI] 1.05-1.45, p = .01) and diagnoses of polymyalgia rheumatica… They were also more likely to have sarcopenia (OR 2.38: 1.80-3.13, p = 9.70 × 10-10) and frailty (OR 2.01: 1.45-2.80, p = 3.41 × 10-05). C282Y homozygote women (n = 312, 0.7%) aged 65-70 were more likely to be frail (OR 1.73: 1.05-2.84, p = .032) and have chronic knee, hip, and back pain" (Tamosauskaite et al., 2019). This continues to solidify the association between musculoskeletal comorbidities and HH and could ultimately contribute to precision medicine approaches to improving quality of life among the elderly.

Hereditary hemochromatosis 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).

VI. Guidelines and Recommendations

United States Preventive Services Task Force (USPSTF)

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 (2006) 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 several 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, 2006).

Canadian Association for the Study of the Liver (CASL) and Choosing Wisely Canada (CWC) Choosing Wisely Canada-Top Five List in Hepatology

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)

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)

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).

o HFE testing is not recommended in patients with
- Unexplained arthritis or arthralgia (1C)
- Type 2 diabetes (1B)."

Guidelines from 2022 recommend that "Individuals with clinical and biochemical signs of haemochromatosis, elevated transferrin saturation and high serum ferritin concentrations, or otherwise unexplained persistently elevated transferrin saturation should be genetically tested for haemochromatosis after informed consent for genetic testing has been obtained (LoE 2, strong recommendation, strong consensus). Patients with increased liver iron evident on liver biopsy or MRI should be clinically assessed and biochemically tested for haemochromatosis (serum ferritin and transferrin saturation) (LoE 2, strong recommendation, strong consensus)" (EASL, 2022).

"Genotyping for p.C282Y in HFE should be carried out in individuals of European origin with biochemical evidence of iron overload (females with transferrin saturation >45% and serum ferritin >200 lg/L and males with transferrin saturation >50% and ferritin >300 lg/L, or otherwise unexplained persistently elevated transferrin saturation) with or without clinical signs or symptoms suggestive of haemochromatosis (LoE 2, strong recommendation, strong consensus). Adult (>18 years of age) first-degree relatives of patients with p.C282Y homozygous haemochromatosis should be tested for the p.C282Y variant in HFE (LoE 4, strong recommendation, strong consensus)" (EASL, 2022).

Regarding 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 the 2022 guidelines EASL (2022) recommends "Adult individuals with a positive family history of first-degree relatives with haemochromatosis should be genetically tested for haemochromatosis after informed consent for genetic testing has been obtained (LoE 4, strong recommendation, strong consensus)."

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)

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)

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; 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)

The ACMG has listed *HFE* genetic testing on its Choosing Wisely list. The ACMG recommends that physicians "Don't order HFE genetic testing for a patient without iron overload or a family history of HFE-associated hereditary hemochromatosis." They expound upon this with the following: "*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. In the setting of genome or exome sequencing, it is now recommended that patients who are homozygous for the pathogenic variant C282Y in HFE should receive this result and consider evaluation" (ACMG, 2021).

British Society for Haematology (BSH)

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 six 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)"

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/medicare-coverage-database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

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 two 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 (2023) 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.

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81256	*HFE* (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D)
81479	Unlisted molecular pathology procedure

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

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X. Review/Revision History

Effective Date	Summary
12/01/2024	Initial Policy Implementation