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| <b>Medical Benefit</b>  |     | <b>Effective Date:</b> 01/01/15  | <b>Next Review Date:</b> 05/21 |
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**Preauthorization is required.**

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

| Populations   | Interventions   | Comparators  | Outcomes   |
|---|---|--|--|
| Individuals:<br>• With abnormal iron indices or clinical signs of iron overload                           | Interventions of interest are:<br>• Genetic testing for HFE | Comparators of interest are:<br>• Standard diagnostic workup without genetic testing | Relevant outcomes include:<br>• Test accuracy<br>• Test validity<br>• Change in disease status |
| Individuals:<br>• Who are asymptomatic with a first-degree relative with known hereditary hemochromatosis | Interventions of interest are:<br>• Genetic testing for HFE | Comparators of interest are:<br>• Standard management without genetic testing        | Relevant outcomes include:<br>• Test accuracy<br>• Test validity<br>• Change in disease status |
| Individuals:<br>• Who are asymptomatic with no family history of hereditary hemochromatosis               | Interventions of interest are:<br>• Genetic testing for HFE | Comparators of interest are:<br>• No genetic screening                               | Relevant outcomes include:<br>• Test accuracy<br>• Test validity<br>• Change in disease status |

### DESCRIPTION

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

### SUMMARY OF EVIDENCE

For individuals who have abnormal iron indices or clinical signs of iron overload who receive genetic testing for HFE, the evidence includes retrospective and prospective observational studies. The relevant outcomes are test accuracy, test validity, and change in disease status. Studies have demonstrated that current genetic testing detects the large majority of HH disease, but that, among those with positive tests (HH homozygotes), penetrance for clinical disease is low. There is no direct evidence of the clinical utility of genetic testing, but, along with prior knowledge of the effectiveness of treatment for clinical iron overload, there is a strong chain of evidence that supports the definitive genetic diagnosis of persons with early signs of HH. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with a first-degree relative with HH who receive genetic testing for HFE, the evidence includes retrospective and prospective observational studies. The relevant outcomes are test accuracy, test validity, and change in disease status. Studies have demonstrated that current genetic testing detects the large majority of HH disease, but that, among those with positive tests (HH homozygotes), penetrance for clinical disease is low. There is no direct evidence of the clinical utility of genetic testing, but, along with prior knowledge of the effectiveness of treatment for clinical iron overload, there is a strong chain of evidence that supports the definitive genetic diagnosis of persons who are first-degree relatives of persons with HH. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with no family history of HH who receive genetic testing for HFE, the evidence includes observational studies of screening in population samples. The relevant outcomes are test accuracy, test validity, and change in disease status. These studies have established population prevalence of genetic HH and serve as partial evidence to estimate penetrance of disease. The low prevalence of HH homozygosity in the general population and incomplete penetrance of clinical disease does not support the clinical utility of genetic testing in an unselected population. The evidence is insufficient to determine the effects of the technology on health outcomes.

## POLICY

Genetic testing for human hemochromatosis (HFE) gene variants may be considered **medically necessary** in a patient with abnormal serum iron indices indicating iron overload. (See Policy Guidelines)

Genetic testing for HFE gene variants may be considered **medically necessary** in individuals with a family history of hemochromatosis in a first-degree relative. (See Policy Guidelines)

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

## POLICY GUIDELINES

### SERUM IRON INDICES IN THE DIAGNOSIS OF HEREDITARY HEMOCHROMATOSIS

Elevated fasting transferrin saturation (the ratio of serum iron to total iron-binding capacity) is the most sensitive initial phenotypic screening test. A minimum cut-off value of 45% will detect almost all affected C282Y homozygotes.

Serum ferritin reflects body iron stores and generally rises later in the progression of iron overload. In the absence of other causes of hyperferritinemia (alcohol abuse, metabolic syndrome, inflammatory states [e.g., infection, cancer, active rheumatoid arthritis], acute and chronic hepatitis), serum ferritin is a good marker of the degree of iron overload.

The negative predictive value of a normal transferrin saturation and serum ferritin is 97%. In this situation, no further testing is recommended.

The 2011 Practice Guidelines by the American Association for the Study of Liver Diseases (AASLD) recommended HFE gene mutation testing in patients with abnormal serum iron indices (i.e., serum ferritin and transferrin saturation), even in the absence of symptoms.

### GENETIC TESTING OF AN INDIVIDUAL WITH A FAMILY HISTORY OF HEREDITARY HEMOCHROMATOSIS

The 2011 practice guidelines by the AASLD recommend screening (iron studies [serum ferritin and transferrin saturation] and HFE variant analysis) of first-degree relatives of patients with HFE-related HH to detect early dis-

ease and prevent complications. For children of an identified proband, HFE testing of the other parent is generally recommended because if results are normal, the child is an obligate heterozygote and need not undergo further testing because there is no increased risk of iron overload.

If C282Y homozygosity or compound heterozygosity is found in adult relatives of a proband, and if serum ferritin levels are increased, then therapeutic phlebotomy can be initiated. If ferritin level is normal in these patients, then yearly follow-up with iron studies is indicated. When identified, C282Y heterozygotes and H63D heterozygotes can be reassured that they are not at risk for developing progressive or symptomatic iron overload. Some individuals with H63D homozygotes can develop mild iron overload.

#### GENETICS NOMENCLATURE UPDATE

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical protocol updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Genome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

| Previous | Updated                    | Definition  |
|----------|----------------------------|---|
| Mutation | Disease-associated variant | Disease-associated change in the DNA sequence   |
|          | Variant                    | Change in the DNA sequence  |
|          | Familial variant           | Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives |

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

| Variant Classification            | Definition   |
|-----------------------------------|--|
| Pathogenic                        | Disease-causing change in the DNA sequence               |
| Likely pathogenic                 | Likely disease-causing change in the DNA sequence        |
| Variant of uncertain significance | Change in DNA sequence with uncertain effects on disease |
| Likely benign                     | Likely benign change in the DNA sequence                 |
| Benign                            | Benign change in the DNA sequence                        |

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology

#### GENETIC COUNSELING

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

## BACKGROUND

### IRON OVERLOAD SYNDROMES

Iron overload syndromes may be hereditary, secondary to another disease (e.g., iron-loading anemias, parenteral iron overload, chronic liver disease, dysmetabolic iron overload syndrome), or due to other miscellaneous conditions (e.g., neonatal iron overload, aceruloplasminemia, congenital atransferrinemia).

Iron overload, if untreated, can lead to secondary tissue damage in a wide range of organs resulting in chronic liver disease (hepatic fibrosis, cirrhosis, hepatocellular carcinoma), endocrine dysfunction (diabetes, hypogonadism), arthralgia or arthritis (typically involving the second and third metacarpophalangeal joints), and cardiomyopathy (with either symptomatic cardiac failure or arrhythmias).

### Hereditary Hemochromatosis

HH, an autosomal recessive disorder, is the most commonly identified genetic disorder in white people, with an estimated prevalence of one in 250. However, fully expressed disease with end-organ manifestations is seen in less than 10% of affected individuals. Factors that influence phenotypic expression of human hemochromatosis (HFE; high iron-related HH [i.e., the clinical appearance of iron overload]) are not defined. Low clinical penetrance may be due to the complex interplay of genetic status and other factors such as age, sex, environmental influences, and comorbid diseases.

HH leads to inappropriate iron absorption from the intestine and progressive increase in intracellular iron concentrations. Untreated HH leads to premature death, usually by liver complications.

### Diagnosis

Patients with hemochromatosis may present with nonspecific systemic symptoms or specific organ-related symptoms, or they may be asymptomatic. Clinical diagnosis of hemochromatosis is based on documentation of increased iron stores as demonstrated by abnormal serum iron indices, specifically elevated transferrin saturation and elevated serum ferritin concentration. Liver biopsy has been used to confirm the diagnosis but is now generally limited to determining the degree of hepatic fibrosis and cirrhosis during disease management. Most patients diagnosed with hemochromatosis will exhibit a familial pattern. However, the familial pattern may not be obvious due to the large percentage of undiagnosed patients in some families, and further evaluation of family members may be required to establish whether a familial pattern is present.

General population screening for HH has been proposed because of the high prevalence of disease, absence of or nonspecific early clinical findings, specificity of findings once they appear, low cost of diagnosis and treatment, and the high cost and low success rate of late diagnosis and treatment. However, because penetrance is low, and the natural history of asymptomatic individuals is unpredictable, support for population-based screening is lacking. A U.S. Preventive Services Task Force (2006) review of the literature suggested that 38% to 50% of individuals with C282Y homozygotes may develop iron overload, with 10% to 33% eventually developing hemochromatosis-associated morbidity.<sup>1</sup> The American Academy of Family Physicians, Centers for Disease Control and Prevention, and U.S. Preventive Services Task Force have recommended against population-based general screening.<sup>1</sup>

### Treatment

Treatment to remove excess iron with serial phlebotomy is simple and effective, and if started before irreversible end-organ damage, restores normal life expectancy. While there has never been a randomized controlled trial comparing phlebotomy with no phlebotomy in the treatment of HH, there is evidence from nonrandomized studies that initiation of phlebotomy before the development of cirrhosis and/or diabetes will significantly reduce HH-associated morbidity and mortality.<sup>2-4</sup>

## Genetics

Most patients with HH have variants in the HFE gene, located on the short arm of chromosome 6. The HFE gene was identified and cloned in 1996. The most common variant in the HFE gene is C282Y, a missense variant that changes cysteine at position 282 in the HFE protein to tyrosine. Homozygosity for the C282Y variant is associated with 60% to 90% of all cases of HH. Additionally, 3% to 8% of affected individuals are heterozygous for this variant. Penetrance for elevated serum iron indices among C282Y homozygotes is variable. However, penetrance for characteristic clinical endpoints (i.e., end-organ damage) is quite low. There is no test that can predict whether an individual with a C282Y homozygote will develop clinical symptoms. A specific variant in PCSK7, which is associated with iron metabolism, has been investigated as a possible predictor of cirrhosis risk in HH patients homozygous for the HFE C282Y variant.<sup>5</sup>

Another significant HFE variant is H63D, which changes histidine at position 63 to aspartic acid. Homozygosity for H63D is insufficient to cause clinically significant iron overload in the absence of modifying factors. However, compound heterozygosity for C282Y/H63D has been associated with increased hepatic iron concentrations; approximately 1% to 2% of patients with this genotype will develop clinical evidence of iron overload, usually in the presence of another liver disease.<sup>6</sup>

The clinical significance of a third HFE variant, S65C (serine at position 65 changed to cysteine), appears to be minimal. This rare variant displays very low penetrance. Compound heterozygosity for C282Y/S65C may confer a low-risk for mild HH. Individuals who are heterozygous for S65C and either the wild-type (normal) or H63D alleles do not seem to be at an increased risk for HH. Other variants in HFE and non-HFE genes (e.g., transferrin receptor 2 [TFR2] gene) resulting in iron overload syndromes are rare.<sup>7-10</sup>

HFE-related HH is now frequently identified by genetic testing in asymptomatic probands and in asymptomatic relatives of patients who are known to have the disease.<sup>2</sup> Therefore, a genetic diagnosis can be made in subjects who have not yet developed phenotypic expression; these subjects have a genetic susceptibility to developing iron overload but may never do so. A 2000 consensus conference of the European Association for the Study of Liver Diseases led to the recognition of different stages and progression of hemochromatosis.<sup>11</sup> These stages were defined as:

1. Stage 1: Patients with “genetic susceptibility” who have the genetic disorder but no increase in iron stores.
2. Stage 2: Patients who have the genetic disorder and phenotypic evidence of iron overload but no tissue or organ damage.
3. Stage 3: Patients who have the genetic disorder with iron overload and iron deposition to the degree that tissue and organ damage occurs.

## REGULATORY STATUS

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

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Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

## REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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