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Medical Policy Manual

Topic: Genetic Testing for Hereditary Hemochromatosis

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Section: Genetic Testing

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hereditary hemochromatosis, a common genetic disorder of iron metabolism, can lead to excessive iron absorption, toxic accumulation, and organ damage. It is an autosomal recessive disorder; therefore, the same genetic mutation must be passed on from both parents (homozygosity) in order for a child to inherit the disease. HH is the most commonly identified genetic disorder in Caucasians, and may be seen in approximately 1 in 250 Caucasians. Untreated HH leads to premature death, usually by liver complications. However, fully expressed disease with end-organ manifestations is seen in <10% of those individuals diagnosed. Treatment by removing excess iron with serial phlebotomy is simple and effective, and if started before irreversible end organ damage, restores normal life expectancy.

Genetic testing is available to assess mutations in the HFE gene, which are responsible for the majority of clinically significant cases of hereditary hemochromatosis. The majority of patients with HH have mutations in the HFE gene, which is on the short arm of chromosome 6. Known mutations associated with this gene are:

- C282Y (associated with 60-90% of all HH cases)
- H63D (heterozygosity for C282Y/H63D are associated with iron overload)
- S65C (rare variant, with low penetrance)

HFE-related HH is now frequently identified in asymptomatic probands and in presymptomatic relatives of patients who are known to have the disease.[1] Therefore, a genetic diagnosis can be applied to

individuals who have not yet developed phenotypic expression. These individuals have a genetic susceptibility to developing iron overload but may never do so.

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were identified. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house ("home-brew") and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

MEDICAL POLICY CRITERIA

I. Genetic testing for HFE gene mutations may be considered **medically necessary** for either of the following:

   A. Patients who meet one or both of the following criteria:

      i. Transferrin saturation ≥ 45% in the absence of confounding causes of hyperferritinemia, including but not limited to alcohol abuse, the metabolic syndrome, inflammatory states, or acute and chronic hepatitis

      ii A first-degree* relative with hemochromatosis

   B. A parent with unknown HFE gene mutation status to determine homozygosity or heterozygosity in a child with one parent known to have hereditary hemochromatosis.

II. Genetic testing for HFE gene mutations is considered **not medically necessary** in children with at least one parent with normal HFE gene mutation status.

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

*First-degree relatives include: parents, siblings, and children of an individual.

SCIENTIFIC EVIDENCE

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

Literature Appraisal

The published literature on genetic testing for HFE gene mutations related to hereditary hemochromatosis (HH) consists of a 2001 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment, two systematic reviews and two non-randomized trials. Recent reviews highlight the pathogenesis, diagnosis and management of HH.[2-4]

Technology Assessments and Systematic Reviews

The 2001 BlueCross BlueShield Technology Evaluation Center (TEC) Assessment on the genetic testing for HFE gene mutations related to HH concluded the following:

- Although randomized controlled trials (RCT) addressing the effect of early phlebotomy therapy in HH patients are limited, studies which assess the predictors of survival in HH patients suggest that survival is improved when phlebotomy therapy is performed adequately, when it is initiated while patients are asymptomatic, before they have progressed to a high degree of iron overload, and before they have developed cirrhosis or diabetes.

- The body of evidence to support genotyping for HH is limited. However, HFE mutation testing was found to improve net health outcomes through the identification of low verses high penetrance mutations. This HFE genotype distinction helps to define the frequency of patient serum marker monitoring. An improvement in patient monitoring could lead to early detection of iron overload in pre-symptomatic patients, which would initiate early phlebotomy treatments.

- Genetic testing and counseling for HFE mutations may improve outcomes in the management of patients with symptoms of iron overload consistent with hereditary hemochromatosis, in the setting of 2 consecutive transferrin saturation values of 45% or more and a serum ferritin value of less than 200–300 mcg/L.

- Genetic testing and counseling for HFE mutations in asymptomatic relatives of individuals with hereditary hemochromatosis also may improve health outcomes.

The Assessment did not address the use of genetic testing for HFE gene mutations in screening of the general population.[5]

In 2008, Bryant and colleagues[6] evaluated the clinical validity and clinical utility of HFA mutation testing in people suspected of having hereditary hemochromatosis and in family members of those diagnosed with the disorder by conducting a systematic review of 15 electronic databases. Studies were included if they reported the use of DNA tests in Caucasians of northern European origin with iron overload suggestive of HH compared with a control population and if they reported or allowed the calculation of sensitivity and specificity.

In total, 11 observational studies were included that could be used to evaluate clinical validity of genotyping for the C282Y mutation in the diagnosis of HH. Criteria used to define hemochromatosis varied between studies. Clinical sensitivity of C282Y homozygosity for HH ranged from 28.4% to 100%; when considering studies that used strict criteria to classify HH, clinical sensitivity ranged from 91.3% to 92.4%. No clinical utility studies were found. The authors concluded that DNA testing for HH in at-risk populations has clinical validity and may have clinical utility.

In 2009, Picot and colleagues conducted a systematic review of the psychosocial aspects of DNA testing for HH in at-risk individuals.[7] Three observational studies met their inclusion criteria and the authors concluded that, while evidence is limited, the results suggest that genetic testing for HH in at-risk individuals is accompanied by few negative psychosocial outcomes.

Randomized Controlled Trials

Although there has never been a randomized controlled trial of phlebotomy versus no phlebotomy in the treatment of HH, there is evidence that initiation of phlebotomy before the development of cirrhosis and/or diabetes will significantly reduce the morbidity and mortality of HH.[1,8,9] In addition, controlled treatment trials are unlikely due to the health risks which would be associated with the control group. Therefore, high quality observational studies are needed.[10]

Non-Randomized Trials

In 2005, Stuhrmann and colleagues[11] initiated a pilot study on DNA-based screening of hereditary hemochromatosis in Germany, to study the analytic validity of different test methods. A total of 3,961 individuals provided blood samples for testing of the HFE mutation C282Y; of these, 3,930 samples were successfully tested with two independent test methods (either polymerase chain reaction [PCR] and restriction digest, reverse allele-specific oligonucleotide hybridization, solid-phase oligonucleotide ligation assay [SPOLA], or microarray [DNA-chip]). In all, 67 of the tested individuals were homozygous for C282Y; 42.6% of the homozygotes already knew their clinical diagnosis of HH before sending the blood sample. Iron accumulation with further signs or symptoms of HH was present in 8 of 34 newly diagnosed C282Y homozygous individuals. Of 7,860 tests performed, 7,841 (99.6%) gave correct results. The overall error rate was 0.24% (95% confidence interval [CI]: 0.15–0.38%). The analytic specificity of the tests methods with respect to the detection of homozygosity for C282Y was 100% (7,726 of 7,726 non-homozygous 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%). The authors concluded that the test methods for C282Y are robust, highly sensitive and specific.

In 2009, McLaren and Gordeuk conducted the Hemochromatosis and Iron Overload Screening (HEIRS) study to evaluate the prevalence, genetic and environmental determinants, and potential clinical, personal, and societal impact of hemochromatosis and iron overload in a multi-ethnic, primary care-based sample of 101,168 adults enrolled over a 2-year period at 4 centers in the U.S. and one in Canada.[12] Initial screening of the participants included genotyping for the HFE C282Y and H63D alleles, serum ferritin, and a calculated transferrin saturation. The yield of HFE genotyping in identifying persons with C282Y homozygosity was low in racial/ethnic groups other than non-Hispanic Caucasians. The overall frequency homozygosity for the C282Y mutation in non-Hispanic Caucasians was 4.4 per 1,000. There was marked heterogeneity of disease expression in C282Y homozygotes. The authors concluded that future studies to discover modifier genes that affect phenotypic expression in C282Y hemochromatosis should help identify patients who are at greatest risk of developing iron overload and who may benefit from continued monitoring of iron status, and that, although genetic testing is well-accepted and associated with minimal risk of discrimination, generalized population screening in a primary care population as performed in the HEIRS study is not recommended.

Clinical Practice Guidelines

American Association for the Study of Liver Diseases (AASLD)

The AASLD recommends:[1]

- "…patients with abnormal iron studies should be evaluated as patients with hemochromatosis, even in the absence of symptoms (strength of recommendation A by the classification used by the Grading of Recommendation Assessment, Development, and Evaluation [GRADE] workgroup)."
- "In a patient with suggestive symptoms, physical findings, or family history of HH, a combination of transferrin saturation and ferritin should be obtained rather than relying on a single test, and if either is abnormal (transferrin saturation ≥45% or ferritin above the upper limit of normal), then HFE mutation analysis should be performed. (Strength of recommendation 1B; Strong; Quality of Evidence: Moderate. Further research may change confidence in the estimate of the clinical effect.)"
- "…screening (iron studies and HFE mutation analysis) of first-degree relatives of patients with *HFE* -related HH to detect early disease and prevent complications. (Strength of recommendation 1A; Strong; Quality of Evidence: High. Further research is unlikely to change confidence in the estimate of the clinical effect.)"
- Screening for non-*HFE*-related HH is not recommended. Average risk population screening for HH is not recommended. (Strength of recommendation 1B; Strong; Quality of Evidence: Moderate. Further research may change confidence in the estimate of the clinical effect.)

American Academy of Family Physicians (AAFP)[13]

In a clinical consensus statement, the AAFP recommends against routine genetic screening for hereditary hemochromatosis in the asymptomatic general population.

Centers for Disease Control (CDC)[14]

The CDC also recommends against population screening for HFE mutations but does indicate that, "genetic testing for HFE mutations can be useful to determine a specific cause for iron overload. In addition, in families with known hereditary hemochromatosis, genetic testing can determine which family members do not have HFE gene mutations."

United States Preventative Services Task Force (USPSTF)[10]

The USPSTF Concluded that research regarding screening for HH is limited and that wide-spread genomic screening has not shown to provide a benefit at this time. These recommendations were based upon a review of the available observational studies.

Summary

The current standard of care for the treatment of hereditary hemochromatosis (HH) is serial phlebotomy, which is effective in restoring normal life expectancy. Mutations in the HFE gene are responsible for the majority of clinically significant cases of HH. Therefore, genetic testing for HFE gene mutations may be considered medically necessary for select patients with abnormal serum iron indices indicating iron overload (transferrin saturation ≥ 45%), as well as in individuals with a family history of hemochromatosis.

Although hereditary hemochromatosis is common, the penetrance of the genotype is low, and the natural history of untreated individuals cannot be predicted. Therefore, genetic testing for hereditary hemochromatosis in screening of the general population is considered investigational.

REFERENCES

1. Bacon, BR, Adams, PC, Kowdley, KV, Powell, LW, Tavill, AS. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology*. 2011 Jul;54(1):328-43. PMID: 21452290
2. Clark, P, Britton, LJ, Powell, LW. The diagnosis and management of hereditary haemochromatosis. *The Clinical biochemist Reviews / Australian Association of Clinical Biochemists*. 2010 Feb;31(1):3-8. PMID: 20179792
3. Gan, EK, Powell, LW, Olynyk, JK. Natural history and management of HFE-hemochromatosis. *Semin Liver Dis*. 2011 Aug;31(3):293-301. PMID: 21901659
4. Alexander, J, Kowdley, KV. HFE-associated hereditary hemochromatosis. *Genet Med*. 2009 May;11(5):307-13. PMID: 19444013
5. TEC Assessment 2001. "Genetic Testing for HFE Gene Mutations Related to Hereditary Hemochromatosis." BlueCross BlueShield Association Technology Evaluation Center, Vol. 16, Tab 22.
6. Bryant, J, Cooper, K, Picot, J, et al. 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*. 2008 Aug;45(8):513-8. PMID: 18310265
7. Picot, J, Bryant, J, Cooper, K, et al. Psychosocial aspects of DNA testing for hereditary hemochromatosis in at-risk individuals: a systematic review. *Genetic testing and molecular biomarkers*. 2009 Feb;13(1):7-14. PMID: 19309267
8. Adams, PC, Speechley, M, Kertesz, AE. Long-term survival analysis in hereditary hemochromatosis. *Gastroenterology*. 1991 Aug;101(2):368-72. PMID: 2065912
9. Niederau, C, Fischer, R, Purschel, A, Stremmel, W, Haussinger, D, Strohmeyer, G. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology*. 1996 Apr;110(4):1107-19. PMID: 8613000
10. Screening for Hereditary Hemochromatosis: A Focused Evidence Review [Internet]. [cited 12/03/2013]; Available from: http://www.ncbi.nlm.nih.gov/books/NBK33436/
11. Stuhrmann, M, Strassburg, C, Schmidtke, J. Genotype-based screening for hereditary haemochromatosis. I: Technical performance, costs and clinical relevance of a German pilot study. *Eur J Hum Genet*. 2005 Jan;13(1):69-78. PMID: 15483651
12. McLaren, GD, Gordeuk, VR. Hereditary hemochromatosis: insights from the Hemochromatosis and Iron Overload Screening (HEIRS) Study. *Hematology Am Soc Hematol Educ Program*. 2009:195-206. PMID: 20008199
13. American Academy of Famliy Physicians (AAFP). Clinical Recommendations. Hemochromatosis. [cited 12/03/2013]; Available from: http://www.aafp.org/patient-care/clinical-recommendations/all/hemochromatosis.html
14. Centers for Disease Control and Prevention (CDC). Training and Education - Epidemiology Prevalence. Hemochromatosis (Iron Storage Disease). [cited 12/03/2013]; Available from: http://www.cdc.gov/ncbddd/hemochromatosis/training/epidemiology/prevalence.html
15. BlueCross BlueShield Association Medical Policy Reference Manual "Genetic Testing for Hereditary Hemochromatosis." Policy No. 2.04.80

CROSS REFERENCES

None

CODES	NUMBER	DESCRIPTION
CPT	81256	HFE (hemochromatosis)(e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D)
HCPCS	None	