Overview

Useful For
Establishing or confirming the clinical diagnosis of hereditary hemochromatosis (HH) in adults

*HFE* genetic testing is NOT recommended for population screening

Testing of individuals with increased transferrin-iron saturation in serum and serum ferritin

With appropriate genetic counseling, predictive testing of individuals who have a family history of HH

**Genetics Test Information**

Detects the 2 common disease-causing mutations: C282Y and H63D. The S65C mutation is reported only when it is observed as part of the C282Y/S65C genotype.

**Highlights**

Molecular testing can be done to establish or confirm the diagnosis of hereditary hemochromatosis in individuals with clinical symptoms.

This test is not recommended for population screening.

This assay will not detect all of the mutations that cause hereditary hemochromatosis.

The S65C mutation is reported only when observed as part of the C282Y/S65C genotype.

**Testing Algorithm**

See [Hereditary Hemochromatosis Algorithm](#) in Special Instructions.

**Special Instructions**

- Molecular Genetics: Congenital Inherited Diseases Patient Information
- Informed Consent for Genetic Testing
- Hereditary Hemochromatosis Algorithm
- Informed Consent for Genetic Testing (Spanish)

**Method Name**

Polymerase Chain Reaction (PCR)-Based Assay Utilizing Agena Mass Array Platform

**NY State Available**

Yes

**Specimen**

**Specimen Type**

Varies
Shipping Instructions
Specimen preferred to arrive within 96 hours of draw.

Specimen Required
Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Specimen Type: Whole blood

Container/Tube:
Preferred: Lavender top (EDTA) or yellow top (ACD)
Acceptable: Any anticoagulant

Specimen Volume: 2.5 mL

Collection Instructions:
1. Invert several times to mix blood.
2. Send specimen in original tube.

Forms
1. New York Clients-Informed consent is required. Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:
   - Informed Consent for Genetic Testing (T576)
   - Informed Consent for Genetic Testing-Spanish (T826)
2. Molecular Genetics: Congenital Inherited Diseases Patient Information (T521) in Special Instructions
3. If not ordering electronically, complete, print, and send a Benign Hematology Test Request Form (T755) with the specimen.

Specimen Minimum Volume
0.5 mL

Reject Due To
All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

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Clinical and Interpretive

Clinical Information

Hereditary hemochromatosis (HH) is an autosomal recessive disorder of iron metabolism with a carrier frequency of approximately 1 in 10 individuals of northern European ancestry. The disease is characterized by an accelerated rate of intestinal iron absorption and progressive iron deposition in various tissues. Iron overload can cause hepatic cirrhosis, hepatocellular carcinoma, diabetes mellitus, arthropathy, and cardiomyopathy. Such complications can generally be prevented by phlebotomy, and patients have a normal life expectancy if treated before organ damage occurs.

For individuals with clinical symptoms consistent with HH or biochemical evidence of iron overload, an HH diagnosis is typically based on the results of transferrin-iron saturation and serum ferritin concentration. Molecular testing can be done to confirm the diagnosis.

The majority of HH patients have mutations in the \textit{HFE} gene. Clinically significant iron overload also can occur in the absence of known \textit{HFE} mutations, so a negative \textit{HFE} test does not exclude a diagnosis of iron overload or hemochromatosis.

The most common mutation in the \textit{HFE} gene is C282Y (exon 4, 845G->A). Homozygosity for the C282Y mutation is associated with 60% to 90% of all cases of HH. Additionally, 3% to 8% of individuals affected with HH are heterozygous for this mutation. These frequencies show variability among different populations, with the highest frequency observed in individuals of northern European ancestry. Penetrance for elevated serum iron indices among C282Y homozygotes is relatively high, but not 100%. However, the penetrance for the characteristic clinical end points (such as diabetes mellitus, hepatic cirrhosis, and cardiomyopathy) is quite low. There is no test that can predict whether a C282Y homozygote will develop clinical symptoms.

The H63D (exon 2, 187C->G) mutation is associated with HH, but the actual clinical effects of this mutation are uncertain. Homozygosity for H63D is insufficient to cause clinically significant iron overload in the absence of additional modifying factors. However, compound heterozygosity for C282Y/H63D has been associated with increased hepatic iron concentrations. Approximately 1% to 2% of individuals with this genotype will develop clinical evidence of iron overload. While individuals with this genotype may have increased iron indices, most will not develop clinical disease without comorbid factors (steatosis, diabetes, or excess alcohol consumption).

The clinical significance of a third \textit{HFE} mutation, S65C (exon 2, 193A->T), appears to be minimal. This rare variant displays a very low penetrance. Compound heterozygosity for C282Y and S65C may confer a low risk for mild HH. Individuals who are heterozygous for S65C and either the wild-type or H63D alleles do not seem to be at an increased risk for HH. The S65C mutation is only reported when it is part of the C282Y/S65C genotype.

See \textit{Hereditary Hemochromatosis Algorithm} in Special Instructions.

Reference Values

An interpretative report will be provided.

Interpretation

An interpretative report will be provided.
For more information about hereditary hemochromatosis testing, see [Hereditary Hemochromatosis Algorithm](#) in Special Instructions.

**Cautions**

This assay will not detect all of the mutations that cause hereditary hemochromatosis. Therefore, the absence of a detectable mutation does not rule out the possibility that an individual is a carrier of or affected with this disease.

Test results should be interpreted in the context of clinical findings, family history, and other laboratory data. Errors in our interpretation of results may occur if information given is inaccurate or incomplete.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

In rare cases, DNA alterations of undetermined significance may be identified.

Because of concerns of the overall penetrance of $HFE$ mutations, $HFE$ genetic testing is not recommended for population screening.

**Clinical Reference**


**Performance**

**Method Description**

A PCR-based assay utilizing Agena Mass Array platform is used to test for the presence of C282Y, H63D, and S65C in the $HFE$ gene. Because the S65C mutation has a minimal effect on iron metabolism, it is only reported when it is found with the C282Y mutation (ie, if the patient has the C282Y/S65C genotype). (Unpublished Mayo method)

**PDF Report**

No

**Day(s) and Time(s) Test Performed**

Monday through Friday; 2 p.m.

**Analytic Time**

6 days

**Maximum Laboratory Time**

7 days
Specimen Retention Time
Whole Blood: 2 weeks (if available) Extracted DNA: 3 months

Performing Laboratory Location
Rochester

Fees and Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information
81256-HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)

LOINC® Information

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