Screening for iron overload: Lessons from the HEEmochromatosis and IRon Overload Screening (HEIRS) Study


BACKGROUND: The HEEmochromatosis and IRon Overload Screening (HEIRS) Study provided data on a racially, ethnically and geographically diverse cohort of participants in North America screened from primary care populations.

METHODS: A total of 101,168 participants were screened by testing for HFE C282Y and H63D mutations, and measuring serum ferritin concentration and transferrin saturation. In the present review, lessons from the HEIRS Study are highlighted in the context of the principles of screening for a medical disease as previously outlined by the World Health Organization.

RESULTS: Genetic testing is well accepted, with minimal risk of discrimination. Transferrin saturation has high biological variability and relatively low sensitivity to detect HFE C282Y homozygotes, which limits its role as a screening test. Symptoms attributable to HFE C282Y homozygosity are no more common in individuals identified by population screening than in control subjects.

CONCLUSIONS: Generalized population screening in a primary care population as performed in the HEIRS Study is not recommended. There may be a role for focused screening in Caucasian men, with some debate regarding genotyping followed by phenotyping, or phenotyping followed by genotyping.

Key Words: Hemochromatosis; HFE; Iron overload

The condition should be considered an important health problem

Hemochromatosis is considered by many physicians to be a rare disease, although with a genetic prevalence of one in 227, it is one of the most common genetic diseases among Northern European populations (1). The case definition of hemochromatosis has been framed in different ways depending on the demonstration of iron overload, a typical genetic test (HFE C282Y homozygosity) or a combination of clinical and biochemical tests (3). The disease has been under-represented on
There should be a test or examination for the condition
Homozygosity of the C282Y mutation in the HFE gene is found in more than 90% of hemochromatosis patients. Transferrin saturation and serum ferritin are not ideal measures for diagnostic screening. Transferrin saturation has considerable biological variability and in the HEIRS study, had a sensitivity of 75%, with a specificity of 95% and positive predictive value of 3.5% for detecting HFE C282Y homozygotes. A fasting sample did not provide any advantages over a random sample (9). Serum ferritin increases with iron overload but also increases with inflammation, fatty liver and alcohol consumption (10). In the HEIRS Study, a large number of Asian, Pacific Islander and African American participants were demonstrated to have elevated serum ferritin, without apparent iron overload (11,12).

The test should be acceptable to the population
Serum transferrin saturation and ferritin testing are widely acceptable to the population. They are also widely used for detection of iron deficiency. These iron measures are routinely requested by physicians who evaluate patients for fatigue, liver abnormalities, anemia and other conditions. Such testing occasionally leads to a diagnosis of hemochromatosis or iron overload. The acceptability of genetic testing for hemochromatosis was less well established at the time of the HEIRS Study. A major innovation of the HEIRS Study was the clear demonstration that genetic testing was highly acceptable to participants from diverse ethnic groups. After one year of follow-up in the study, there was no evidence of genetic discrimination (13). Most participants were satisfied to be notified of their genetic test results by mail (14,15).

The natural history of the disease should be adequately understood
During the HEIRS Study, several large, long-term epidemiological studies with stored DNA reported clinical outcomes in relation to genetic testing for HFE gene mutations. This allowed for a glimpse of the natural history of untreated disease in HFE hemochromatosis. It is apparent in all of these studies that a progressive rise in serum ferritin is not inevitable in hemochromatosis, and many HFE C282Y homozygotes appear to have a plateau in serum ferritin or a decrease in ferritin over time (8,16,17). These observations have strongly diminished the enthusiasm for population screening for hemochromatosis because there is little evidence of differences in clinical outcome between screened and unscreened groups to justify the intervention of the screening. This does not imply that there are no patients with severe complications of iron overload. These patients were being referred and treated by many of the HEIRS investigators at the same time as asymptomatic C282Y homozygotes were being identified in their communities through the HEIRS screening. Emerging information suggests that many of these milder cases may not develop symptoms or complications of iron overload, regardless of whether they are treated with phlebotomy.

There should be an agreed policy on who to treat
Because it is unclear which individuals with hemochromatosis will develop complications of iron overload, it has been a standard practice to offer iron depletion by phlebotomy to all patients with an elevated serum ferritin (greater than 200 µg/L

### TABLE 1
Lessons from the HEmochromatosis and IRon Overload Screening (HEIRS) Study

<table>
<thead>
<tr>
<th>Description</th>
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<tbody>
<tr>
<td>Generalized population screening in a primary care population as performed in the HEIRS Study is not recommended</td>
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<tr>
<td>Genetic testing is well accepted, with minimal risk of discrimination (13)</td>
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<tr>
<td>An elevated serum ferritin is very common, particularly in Asians, Pacific Islanders and African Americans, and may not be an indication for phlebotomy. In the absence of HFE C282Y homozygosity, this finding usually does not represent an increase of iron stores of &gt;4 g (11)</td>
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<tr>
<td>Transferrin saturation has high biological variability and relatively low sensitivity to detect HFE C282Y homozygotes, which limits its role as a screening test (9)</td>
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<tr>
<td>Most symptoms typically attributed to HFE C282Y homozygosity are no more common in individuals identified by population screening than in control subjects lacking HFE mutations (6)</td>
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<tr>
<td>Mild increases in body iron stores in the range of 2 g to 3 g are common in non-HFE C282Y homozygotes, but iron overload, defined as iron stores &gt;4 g, is most common in Caucasian men who are HFE C282Y homozygotes (22)</td>
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<tr>
<td>There may be a role for focused screening in Caucasian men with some debate about whether to perform genotyping followed by phenotyping or, phenotyping followed by genotyping (23)</td>
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hospital discharge and death data, and is an uncommon indication for liver transplantation. Treatment of the major medical complications of hemochromatosis, such as cirrhosis of the liver and hepatocellular carcinoma, are costly but these occur in a small fraction of HFE C282Y homozygotes. Population-based studies estimate that approximately 5% of male HFE C282Y homozygotes may have cirrhosis (4,5), and hepatocellular carcinoma may occur in 10% of cirrhotic patients. Most patients identified in population-based hemochromatosis screening studies are asymptomatic (6).

There should be a treatment for the condition
Iron depletion by phlebotomy is a well-recognized treatment for iron overload associated with hemochromatosis. Recent studies have demonstrated a reversal of hepatic fibrosis by phlebotomy, which is the strongest evidence to support this therapy (7). There have been no randomized trials to evaluate the benefits of phlebotomy therapy and most experts believe that such a trial would be unethical.

Facilities for diagnosis and treatment should be available
The diagnosis of hemochromatosis can be made with iron tests such as serum transferrin saturation and ferritin, and a genetic test for the C282Y mutation in the HFE gene. These tests are widely available. Liver biopsy is no longer required as a diagnostic test in an HFE C282Y homozygote. Many jurisdictions allow healthy hemochromatosis patients to become voluntary blood donors.

There should be a latent stage of the disease
Biochemical abnormalities in transferrin saturation may precede clinical signs and symptoms by 40 to 50 years. Genetic testing has the potential to identify individuals who are at increased risk of developing iron overload. It can be difficult to predict which C282Y homozygotes develop progressive iron overload with liver damage (8).
in women, greater than 300 µg/L in men). However, in light of the epidemiological studies, the prognosis of participants with mild iron overload may be excellent without any iron-depleting treatment. Less is known about non-HFE or nonclassical hemochromatosis. Therefore, there are uncertainties regarding the need and rationale for treating all patients and, thus, the justification for widespread screening is unconvincing.

The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole

The HEIRS Study was not designed to analyze screening and medical follow-up costs and charges. Cost-effectiveness studies should reveal an incremental benefit in the screened group compared with the unscreened group to justify any costs associated with screening and follow-up (including follow-up of incidental findings, other illness and iron deficiency). These concepts have been explored in previous studies that have used HEIRS Study data regarding the prevalence of cirrhosis (18-20). The conclusions of these studies have been mostly supportive of screening but have not been widely accepted by public health and policy groups.

Case-finding should be a continuous process, not just a ‘once and for all’ project

It seems unlikely that screening for hemochromatosis would ever be endorsed for all North Americans and performed in a centralized way as in the HEIRS Study, regardless of ethnicity. The highest risk group identified in the HEIRS Study was Caucasian men. To focus on this group for systematic hemochromatosis testing would improve screening efficiency but accessing this subpopulation remains challenging because men tend not to have regular interactions with primary care providers. Testing at the time of periodic assessments of cholesterol, prostate-specific antigen or blood pressure has some merit but would likely only capture a small percentage of cases. It is more likely that the diagnosis would be made incidentally in most cases. Once a patient is discovered, a family history and pedigree investigation is an important aspect of management in detecting at risk individuals who may benefit from additional evaluation (21). Increasing physician and patient awareness may be the best strategy to improve the rate of early diagnosis and treatment of hemochromatosis.

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