Phenotype

2 occasions
definition:elevated fasting TS on

0.60 [men]
without other known causes

Simultaneous genetic and

0.50
NA
NA

HFE

C283Y and

HFE

(alleles C282Y and H63D; phenotypic testing using TS; SF measurement

Iron overload:

H63D mutations, serum iron, SF

elevated SF level (>300 µg/L [men] and >100 µg/L [women]), increased hepatic iron content determined by using hepatic biopsy, or iron >4 g (mobilized by TP)

No genetic criteria used

Hepatic cirrhosis and diabetes criteria not reported

1st- and 2nd-degree relatives, C282Y/C282Y homozygotes:

25 of 112 (calculated)

Phenotype, n/n (%):

C282Y/C282Y homozygotes, Other, n/n (%): 29 of 112 (calculated)

Siblings: 14/42 (33)

Parents: 3/16 (19)

Other blood relatives: 3/16 (19)

22 of 61 probands; blood relative with hereditary HC (36%); all were C282Y/C282Y

Phenotype, n/n (%):

C282Y/C282Y homozygotes during routine

Other targeted screening

Cadet et al., 2003 (61)
Multiple settings: primary care patients were recruited from 3 Oxfordshire practices, and secondary care patients were recruited from patients attending specialist clinics at Amiens University Hospital
No dates reported France

Cohort study: to determine the optimal means of identifying patients with undiagnosed hereditary HC, using HFE genotype or phenotype

Primary care: 4022 consultations, during which 168 patients were identified with an index symptom (diabetes, AR, unexplained fatigue, abdominal pain, liver disease, abnormal LFT results, impotence, premature atherosclerosis, or cardiac arrhythmia), of whom 88 were age 25–70 y and offered a genetic test for HC; 60 patients were tested Secondary care: Several groups of patients attending specialist clinics at a hospital
Rheumatology clinics: 221 rheumatoid factor-negative patients with OS or AR
Endocrinology clinics: 121 diabetic patients from 1 endocrine department

Patients with presenting conditions possibly related to HC

Case-patients:

Exclusions: families or patient previously diagnosed with hereditary HC
Controls:

Inclusion: age >18 y
Living in Picardy
Attended a free health checkup clinic

Case-patients:

OS

n = 119
sex: NR
Age: 64 (SD, 12 y)
AR

n = 62
Sex: NR
Age: 61.3 (SD, 13.9)

Diabetes

n = 121
Women: n = 42
Men: n = 79
Age: 54.8 (SD, 8.3)

F/A

n = 227
Women: n = 144
Men: n = 83
Age: 58.3 (SD, 15.6)

Cases: n = 991

HFE C282Y and H63D mutations, serum iron, SF

NA

NA

Pheno HV PC OS + AR DM F/A

TS > 0.40, % Pts w/

TS > 0.40 who are YY, n/n (%)

SF >300 µg/L %
Pts with SF >300 µg/L who are YY, n/n (%)

4/92 (4.3)

3/19 NR

2/36 (5.6)

8/84 (9.5)

2/23 NR

1/9 (11.1)

1/36 (2.8)

0/6 NR

1/9 (11.1)

0/6 (0)

13/70

13/75

13/75

Table Appendix 10. Studies of High-Risk Groups for C282Y Homozygosity or Hereditary Hemochromatosis*

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Setting, Time Frame, Country</th>
<th>Study Design</th>
<th>Sample</th>
<th>Risk Group Definition</th>
<th>Inclusion and Exclusion Criteria</th>
<th>Population</th>
<th>Initial Screening Sequence</th>
<th>Definition of Clinical HC</th>
<th>Diagnostic Criteria</th>
<th>Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family setting</td>
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<tr>
<td>Barton et al., 1999 (57)</td>
<td>Southern Iron Disorder Center and Brookwood Medical Center No dates reported United States</td>
<td>Cross-sectional study: to compare phenotyping and HFE genotyping for diagnosis of hereditary HC in 150 family members of 61 probands</td>
<td>Proband diagnosed by medical care delivery from June 1996 to June 1998 (Genetic testing not used to diagnose probands before family members were identified)—only 73.8% were C282Y/C282Y homozygotes 150 family members of 61 probands (did not report what percentage of total)</td>
<td>Relatives of people with iron overload (probands): 16% had cirrhosis and 5% had diabetes attributable to iron overload</td>
<td>Inclusion: willingness of probands and a family member to partake Exclusions: NR</td>
<td>72 (48%) men 78 (52%) women Mean age, 46 (SD, 15) y (All were adults excluding one 11-year-old) 94 were 1st-degree relatives; 56 were 2nd-degree non-blood relatives</td>
<td>Simultaneous genetic testing for HFE alleles C282Y and H63D; phenotype testing using TS; SF measurement</td>
<td>Phenotype definition: elevated fasting TS on ≥ 2 occasions without other known causes (&gt;0.60 [men] and &gt;0.50 [women])</td>
<td>Iron overload: elevated SF level (&gt;300 µg/L [men] and &gt;100 µg/L [women]), increased hepatic iron content determined by using hepatic biopsy, or iron &gt;4 g (mobilized by TP)</td>
<td>No genetic criteria used</td>
<td>Hepatic cirrhosis and diabetes criteria not reported</td>
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*Studies of High-Risk Groups for C282Y Homozygosity or Hereditary Hemochromatosis

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<th>Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional</td>
<td>1st-degree relatives: 30/94 (33) Non–first-degree relatives: 4/56 (7.1)</td>
<td>phenotype: presence of elevated TS or iron overload or both</td>
<td>22 of 61 probands; blood relative with hereditary HC (36%); all were C282Y/C282Y</td>
<td>Phenotype, n/n (%):</td>
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</tbody>
</table>
### Appendix Table 10—Continued

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Setting, Time Frame, Country</th>
<th>Study Design</th>
<th>Sample (including those with unstable diabetes)</th>
<th>Risk Group Definition</th>
<th>Population</th>
<th>Inclusion and Exclusion Criteria</th>
<th>Initial Screening Sequence</th>
<th>Definition of Clinical HC</th>
<th>Diagnostic Criteria</th>
<th>Results Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deugnier et al., 2002 (51)</td>
<td>Internal medicine clinics: 227 patients with chronic fatigue and AR Controls: recruited from 2337 persons &gt;18 y from health appraisal center</td>
<td>Cross-sectional study</td>
<td>Men: age 25–40 y Women: age 35–50 y</td>
<td>Family history of iron excess Chronic fatigue Increased ALT levels</td>
<td>Included: Attending Health Appraisal Centre; meeting age criteria Those who declined genotyping (4%) had no personal history of iron excess</td>
<td>n = 9396 (96% of total population)</td>
<td>Men: n = 3367 Women: n = 6029</td>
<td>Questionnaire; age, sex, BMI, smoking history, presence of chronic fatigue, chronic AR, diabetes</td>
<td>HFE C282Y mutation testing</td>
<td>C282Y homozygotes by family history of iron excess, n/n (%): Men Family history: 3/383 (3.6) (calculated) No family history: 7/3904 (0.2) (calculated) Women Family history: 12/175 (7%) (calculated) No family history: 21/175 (12) (calculated)</td>
</tr>
<tr>
<td>CHD, CAD</td>
<td>Waalen et al., 2002 (62)</td>
<td>Health appraisal center in San Diego, California May 1999–August 2001 United States</td>
<td>Cross-sectional study: to examine the relationship between 2 HFE mutations (C282Y and H63D) and the prevalence of CHD in a large white adult population</td>
<td>n = 35 792 All white, non-Hispanic adult patients age ≥25 y who attended a health appraisal center between May 1999 and August 2001</td>
<td>History of CHD, defined as &quot;yes&quot; to questions &quot;Have you had a heart attack for which you were hospitalized for at least 3 days?&quot; or &quot;Do you have angina pectoris?&quot; or an ICD-9 code of 410 or 412 in the medical record</td>
<td>n = 15 362 n = 15 554 All participants were white, non-Hispanic</td>
<td>400-item questionnaire supplemented with medical record review to ensure ascertainment of all CHD events Serum iron, TS, and SF values</td>
<td>NA</td>
<td>C282Y/C282Y, n/n (%): Men CHD: 3/1796 (0.17) No CHD: 65/8540 (0.76) Women CHD: 3/1074 (0.28) No CHD: 65/9117 (0.71)</td>
<td>Good</td>
</tr>
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### Appendix Table 10—Continued

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<tr>
<td>Liver disease clinics</td>
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<tr>
<td>Poullis et al., 2003 (63)</td>
<td>Patients attending a liver clinic at a teaching district general hospital in south London 1997–2001, United Kingdom</td>
<td>Cross-sectional data: to examine the value of routine TS testing of new liver clinic attendees over a 5-y period in detecting previously unrecognized cases of hereditary HC</td>
<td>667 outpatients referred for investigation of liver disease over 5 y</td>
<td>Afro-Caribbean/African: ND; Asian: majority originated from the Indian subcontinent, but also included 2 Chinese persons and 4 Iranian persons; Mediterranean: families originated from Portugal and countries bordering the Mediterranean Sea; Northern European: ND; Celtic: parents or grandparents from Cornwall, Wales, Scotland, or Ireland</td>
<td>Outpatients referred to a liver clinic for investigation of liver disease</td>
<td>n = 667</td>
<td>Nonfasting TS; those with TS &gt;0.45 or a liver biopsy had HFE genotyping indications for biopsy included C282Y homozygosity, C282Y/H63D compound heterozygosity, elevated TS (&gt;0.60), unexplained parenchymal liver disease, persistently abnormal LFT results, and liver disease of known cause necessitating staging or assessment of disease progression</td>
<td>NA</td>
<td>TS cutoffs</td>
<td>Fair</td>
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<tr>
<td>Moodie et al., 2002 (64)</td>
<td>Specimens of patients with arthritis from the DNA archive of NOAR First diagnosed between 1989 and 1995, United Kingdom</td>
<td>Case-control study: to determine the value of screening patients with inflammatory arthritis for hereditary HC- associated mutations in the HFE gene</td>
<td>People with inflammatory arthritis</td>
<td>Unaffected inflammatory arthritis population collected by NOAR; prevalence of the hereditary HC-associated HFE genotypes compared with that in a large sample from unaffected populations</td>
<td>People with inflammatory arthritis</td>
<td>n = 1000 Controls: 373 unaffected volunteers from screening trial and 541 patients undergoing full blood counts Controls: Patients with HC and people with foreign names</td>
<td>NA</td>
<td>HFE C282Y and H63D mutation testing</td>
<td>NA</td>
<td>Good</td>
</tr>
<tr>
<td>Arthritis Willis et al., 2002 (65)</td>
<td>Specimens of patients with arthritis from the DNA archive of NOAR First diagnosed between 1989 and 1995, United Kingdom</td>
<td>Case-control study: to determine the value of screening patients with inflammatory arthritis for hereditary HC- associated mutations in the HFE gene</td>
<td>People with inflammatory arthritis</td>
<td>Unaffected inflammatory arthritis population collected by NOAR; prevalence of the hereditary HC-associated HFE genotypes compared with that in a large sample from unaffected populations</td>
<td>People with inflammatory arthritis</td>
<td>n = 1000 Controls: 373 unaffected volunteers from screening trial and 541 patients undergoing full blood counts Controls: Patients with HC and people with foreign names</td>
<td>Variable</td>
<td>Arthritic Patients: 54 patients 1 in 287 (190–403) Controls: 54 patients 1 in 236 (170–335)</td>
<td>NA</td>
<td>Good</td>
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<tr>
<td>Swinkels et al., 2002 (66)</td>
<td>Department of General Internal Medicine of the University Medical Centre St. Radboud, Nijmegen, a Dutch tertiary CFS referral center 1992 The Netherlands</td>
<td>Cross-sectional study: to determine whether patients previously diagnosed as having CFS actually have primary HC</td>
<td>NR</td>
<td>Patients fulfilling criteria for CFS Patients had given permission to store serum for future CFS studies</td>
<td>NR</td>
<td>88 self-referred patients previously diagnosed with CFS Mean age, 40 y (range, 20–66 y) Men: n = 23 Women: n = 65</td>
<td>TS: elevated if &gt;0.40 (women) and &gt;0.45 (men) All patients who could be located with elevated TS (15 of 19) were asked to provide a new fasting blood sample for a second TS and SF Genotyping done if TS or SF levels were elevated (reference values: SF: 15–280 g/L [men], 6–80 g/L [premenopausal women], and 15–190 g/L [postmenopausal women]) Elevated TS: n = 6 Elevated SF level: n = 2 Elevated TS and SF level: n = 0</td>
<td>NA</td>
<td>NR</td>
<td>None of the 8 patients with increased TS or increased SF levels were C282Y homozygotes or compound C282Y/H63D heterozygotes</td>
</tr>
</tbody>
</table>

* ALT = alanine aminotransferase; AR = arthropathy; BMI = body mass index; CAD = coronary artery disease; CFS = chronic fatigue syndrome; CHD = coronary heart disease; DD/CC = H63D homozygous; DM = diabetes mellitus; F/A = fatigue and arthralgia; Geno = genotype; HC = hemochromatosis; HD/CC = H63D heterozygous; HD/CY = compound heterozygous; HH/CC = wild type; HH/CY = C282Y heterozygous; HH/YY = C282Y homozygous; HMO = health maintenance organization; HV = healthy volunteer; ICD-9 = International Classification of Diseases, Ninth Revision; LFT = liver function test; NA = not applicable; ND = not determined; NOAR = Norfolk Arthritis Register; NR = not reported; OS = osteoporosis; PC = primary care; Pheno = phenotype; Pts = patients; TP = therapeutic phlebotomy; TS = transferrin saturation; YY = C282Y/C282Y.

† Values are percentages.
‡ P ≤ 0.001; chi-square test was used to determine the significance in each genotype versus healthy volunteers.
§ P < 0.01; chi-square test was used to determine the significance in each genotype versus healthy volunteers.