

Screening Primary Care Patients for Hereditary Hemochromatosis with Transferrin Saturation and Serum Ferritin Level: Systematic Review for the American College of Physicians

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Background: Therapeutic phlebotomy for hereditary hemochromatosis is relatively safe and presumably efficacious when offered before cirrhosis develops, so screening primary care patients is of substantial interest.

Purpose: To conduct a systematic review of the evidence on 1) the prevalence of the disease in primary care, 2) the risk for morbid or fatal complications for untreated patients, 3) the diagnostic usefulness of transferrin saturation and serum ferritin level in identifying early disease, 4) the efficacy of early treatment, and 5) whether the benefits of screening outweigh the risks.

Data Sources: MEDLINE search from 1966 through April 2004, complemented by reference review of identified original studies and review articles published in English.

Study Selection: PubMed Clinical Queries filters search of prognosis, diagnosis, etiology, or treatment were used depending on the question. Two authors reviewed all titles and abstracts.

Data Extraction: Two investigators independently reviewed extracted data.

Data Synthesis: The prevalence of hereditary hemochromatosis was 1 in 169 patients to 1 in 556 patients ($n = 3$ studies). Uncontrolled, prospective studies of genetic homozygous patients did not consistently identify a link to overt hereditary hemochromatosis. A serum ferritin level less than 1000 $\mu\text{g/L}$ was predictive of absence of cirrhosis. Six studies demonstrated reduced survival in patients with cirrhosis. Diagnostic studies varied with respect to case definition. No blinded, independent comparisons of screening tests with the gold standard (biopsy or results of quantitative phlebotomy) or randomized, controlled trials of phlebotomy were identified. Cost-effectiveness analysis was limited by lack of prospective data on the natural history of the disease.

Limitations: Varied case definition and lack of prospective cohort studies or randomized trials.

Conclusions: The available evidence does not demonstrate that benefits outweigh the risks and costs of screening for hemochromatosis.

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Hereditary hemochromatosis is a genetic disorder of iron metabolism resulting in excessive iron overload and is associated with clinically significant morbid and fatal complications related to tissue iron deposition (1). It is an autosomal recessive disorder linked to a mutation of the *HFE* gene on the short arm of chromosome 6. This gene is the result of a single base change in which tyrosine is substituted for cysteine at position 282 of the HFE protein (C282Y). Available evidence strongly supports an association of the C282Y mutation with hereditary hemochromatosis, although other mutations in *HFE* have been identified. The substitution of aspartic acid for histidine at position 63 (H63D) has been observed but has limited clinical effect (2). Several genetic mutations are also linked to juvenile hereditary hemochromatosis (3, 4).

The C282Y mutation is variably and unpredictably associated with phenotypic changes of iron overload that include elevated transferrin saturation and serum ferritin levels. An increasing transferrin saturation is the earliest detectable biochemical abnormality in hereditary hemochromatosis and is attributed to increased intestinal iron absorption (4). Enterocytes aberrantly continue to transfer iron from the gut into the bloodstream rather than store the iron as ferritin. The role of *HFE* in this pathophysiological process is not fully clear. Some patients with the *HFE* gene never progress beyond this biochemical abnormality. However, progressive iron overload occurs in others. Marked elevation of serum ferritin level has been associated

with histologic evidence of iron deposition (5). The morbid complications of hereditary hemochromatosis are the result of tissue deposition, and they develop late in its course. They include arthritis, diabetes mellitus, congestive heart failure, cirrhosis, and hepatocellular carcinoma (6). Liver iron deposition with cirrhosis is associated with reduced survival (7).

The estimated prevalence of hereditary hemochromatosis is 1 in 200 persons to 1 in 250 persons in the general population, making hereditary hemochromatosis one of the most common genetic disorders (8). However, the prevalence of hereditary hemochromatosis varies depending on the case definition of disease (9). With genetic testing of populations originating in northern Europe, approx-

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imately 0.5% is homozygous for the C282Y mutation (10). With phenotypic screening, 1% to 6% of the U.S. population have elevated transferrin saturation levels, and 11% to 22% of them have concomitant elevations of their serum ferritin levels (11).

Over the past decade, interest in promoting general population screening for hereditary hemochromatosis has increased (12, 13). Advances in genetic testing, changing definitions of the disease that include earlier stages of iron overload, increased appreciation of the prevalence and importance of the disease, and the presumed effectiveness of a simple intervention (phlebotomy) have prompted a debate on the benefits and risks of a screening intervention program in the United States. The use of genetic testing to screen family members of individuals identified with hereditary hemochromatosis seems to be cost-effective (14). The benefit in primary care is less clear. In 1997, the Centers for Disease Control and Prevention and the National Institutes of Health sponsored a meeting on iron overload, public health, and genetics (15). A result of the conference was a published review of the evidence for hemochromatosis screening (13). Evidence for screening was evaluated against the U.S. Preventive Services Task Force criteria (16). Little evidence was available to support the efficacy of genetic testing, and there were substantial ethical, legal, and social concerns. Likewise, evidence was insufficient to support the use of transferrin saturation, and few comparative data were available to establish the magnitude and clinical significance of risk in patients with various levels of iron overload. However, others argued for expanded screening and have targeted primary care physicians for

educational intervention to improve awareness of the disease (12, 17). The Working Group on Research Priorities identified the evidence that is most needed to provide a scientific basis for population screening (18). They identified the need for research to characterize the natural history of the relationship between genotype and phenotype in hereditary hemochromatosis and other iron overload disorders. They also identified 3 additional priorities: 1) development of an optimal approach for screening for iron overload; 2) analyses of the cost-effectiveness of screening; and 3) assessment of the ethical, legal, and social implications of screening. Given this background, we must examine the current evidence and determine whether it now supports general population screening for hereditary hemochromatosis.

To promote screening within the primary care setting, one must demonstrate that the disease is common, the burden is substantial, the treatment is efficacious, the screening tests are accurate, the screening is effective, and the benefits of screening outweigh the risks (16). We evaluate the evidence to support screening within the primary care setting. Because of the controversy surrounding genetic testing as a screening tool (low penetrance of hereditary hemochromatosis and lack of complete identification of genetic mutations associated with hereditary hemochromatosis), our review focuses on the phenotypic measures that are most likely to be useful in primary care: transferrin saturation and serum ferritin level. To evaluate the evidence, we address each key question that is relevant to a screening intervention.

Table 1. Prevalence of Hereditary Hemochromatosis in Primary Care Settings*

Study, Year (Reference)	Setting	Sampling Approach	Sample Characteristics	Definitive HHT	Reported HH	Ceiling Estimate of HH†	Cirrhosis
Baer et al., 1995 (20)	Oakland Kaiser Permanente	Consecutive men > 30 y of age	n = 3977; median age, 54 y	n = 12 (0.30%): 9 (0.46%) white men (n = 1974) (mean age, 54.4 y); 2 (0.17%) black men (n = 1148); 1 (0.14%) other (n = 725)	n = 8 (0.2%): 7 (0.35%) white men; 0 black men; 1 (0.14%) other	n = 15 (0.38%): 11 (0.56%) white men; 3 (0.26%) black men; 1 (0.14%) other	n = 0
Phatak et al., 1998 (21)	22 primary care practices in Rochester, New York	All adults ≥ 18 y of age	n = 16 051 (19%–94% of eligible patients across practices); median age of white patients, 54 y; median age of nonwhite patients, 43–45 y; 42% men	n = 29 (0.18%): 20 (0.37%) white men (n = 5356); 0 nonwhite men (n = 1349); 9 (0.13%) white women (n = 7099); 0 nonwhite women (n = 2227)	n = 47 (0.29%): 28 (0.52%) white men; 1 (0.07%) nonwhite man; 18 (0.25%) white women; 0 nonwhite women	n = 59 (0.37%): 41 (0.77%) white men; 0 nonwhite men; 18 (0.25%) white women; 0 nonwhite women	n = 3 (0.019%)
Niederlau et al., 1998 (22)	9 primary care practices in West Germany	Every third primary care patient	n = 3027 (95% eligible); age, NA; 40.6% men	n = 18 (0.59%) (mean age, 54.5 y): 13 (1.05%) men (mean age, 55 y); 5 (0.28%) women (mean age, 53 y)	n = 53.4 (1.8%): 19.5 (1.6%) men; 33.9 (1.9%) women	n = 24 (0.79%)	n = 4 (1 with hepatocellular carcinoma)

* HH = hereditary hemochromatosis; NA = not applicable.

† Definitive HH requires liver biopsy with hepatic iron concentration > 30 mmol/kg dry weight or >2000 mg of iron stores by phlebotomy.

‡ Determined by application of HH criteria to those with repeated elevations of transferrin saturation and serum ferritin level who did not undergo liver biopsy or phlebotomy.

METHODS

We conducted a systematic review for each question in MEDLINE for papers published from 1966 through April 2004 by using PubMed Clinical Queries filters for a sensitive search of prognosis, diagnosis, etiology, or treatment depending on the question. We included only English-language studies. Two reviewers independently reviewed all abstracts. A third reviewer resolved conflicts about inclusion of an article. We also manually searched references from included studies. The Appendix (available at www.annals.org) includes details for conducting the search for each subquestion. We assessed methodologic quality of studies for a specific question by using accepted epidemiologic criteria (19). We did not use any formal method of quality assessment or scoring.

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RESULTS

Subquestion 1: What Is the Prevalence of Hereditary Hemochromatosis in the Primary Care Setting?

We identified 3 prevalence studies in primary care settings (Table 1) and 12 studies in various general population settings (Table 2) (Appendix Figure 1, available at www.annals.org). Because of variability among studies, we examined the prevalence data in 3 ways: use of the strict definition recommended in the Hemochromatosis and Iron Overload Screening (HEIRS) study (34); use of the prevalence reported by the investigator(s); and use of a ceiling estimate, which assumed that the many study participants with elevated transferrin saturation and serum ferritin levels who declined liver biopsy or therapeutic phlebotomy had the same probability of primary iron overload as those who were actually evaluated.

Using strict criteria, we found that the prevalence of hereditary hemochromatosis within a primary care setting was 0.18% to 0.59% (1 in 169 patients screened to 1 in 556 patients screened). The prevalence reported by the investigators was 0.2% to 1.8% (1 in 56 patients screened to 1 in 500 patients screened). We estimated the ceiling prevalence of hereditary hemochromatosis to be 0.37% to 0.79% (1 in 127 patients screened to 1 in 270 patients screened). Most patients with hereditary hemochromatosis did not have concomitant cirrhosis. Using the HEIRS study definition, we found that hereditary hemochromatosis prevalence was higher in white men (0.37% to 0.46%) than nonwhite men (0% to 0.17%) and was higher in men than women.

Using strict criteria, we estimated the prevalence of hereditary hemochromatosis from the 2 general population studies (23, 24) to be 0.16% to 0.28% (1 in 357 patients screened to 1 in 625 patients screened). The investiga-

tors reported higher rates—as high as 0.74% in Norwegian men. In screening employees or blood donors, the prevalence of hereditary hemochromatosis was higher in men than women and, when demographic data were available, was higher in white men than nonwhite men (Table 2).

Within the primary care setting ($n = 23\,055$) and using strict criteria, we identified hereditary hemochromatosis in 59 patients (0.13%) (equivalent to 1 in 795 screened patients). Of these 59 patients, 55 patients (93%) were 40 years of age or older, 46 patients (78%) were men, and 38 patients (93%) in the 2 studies that provided racial characteristics were white. Fifty-two of 59 patients (88%) did not have cirrhosis. These data demonstrate that the prevalence of hereditary hemochromatosis varies across different subgroups determined by race, sex, and age. The highest prevalence of hereditary hemochromatosis detected by screening within primary care seems to be in white men, probably ranging between 1 of 185 screened patients and 1 of 219 screened patients (20, 21). Screening that targeted white men 40 years of age or older would further increase the prevalence of hereditary hemochromatosis.

Subquestion 2: In Asymptomatic Patients with Hereditary Hemochromatosis, What Is the Risk for Developing Morbid Complications or for Death?

The definition of iron overload varied across studies. Some studies evaluated the relationship between the asymptomatic elevation of transferrin saturation and serum ferritin levels and the development of disease, while other studies addressed the relationship between iron tissue deposition and the development of complications and death. Consequently, we separately aggregated the evidence to address these 2 related but different ways of characterizing iron overload.

The Relationship between Transferrin Saturation–Serum Ferritin Level and Hereditary Hemochromatosis–Related Disease

We identified 11 studies (5, 35–44) for inclusion (Appendix Figure 2, available at www.annals.org). None was a prospective cohort study comparing survival or complications in patients with and without hereditary hemochromatosis defined by an elevated serum ferritin level.

Three uncontrolled, prospective studies (35–37) examined the change of iron stores over time in individuals identified as being C282Y homozygotes (Table 3). One study (35) followed 12 Australian patients for 17 years. While the median transferrin saturation and ferritin level increased, some patients had constant levels and some had decreasing ferritin levels. In a Canadian study of 22 participants, Yamashita and Adams (36) observed a decrease in serum ferritin levels in 13 patients and serum ferritin levels remaining less than the upper limit of normal in 20 patients after a median of 4 years. In the Copenhagen City Heart Study (37), average transferrin saturation levels in-

Table 2. Prevalence of Hereditary Hemochromatosis in Various General Population Settings*

Study, Year (Reference)	Setting	Sampling Approach	Sample Characteristics	Definitive HH†	Reported HH	Ceiling Estimate of HH‡	Cirrhosis
Burt et al., 1998 (23)	General population (Christchurch, New Zealand)	Random sample of adults ≥ 18 y of age	$n = 1065$ (represents 30.3% of all invited; mean age, 50.2 y): 423 men; 641 women	$n = 3$ (0.28%): 1 (0.24%) man (age, 71 y); 2 (0.31%) women (age, 38 y)	$n = 3$ (0.28%): 1 (0.24%) man; 2 (0.31%) women	ND	$n = 0$
Asberg et al., 2001 (24)	General population (Norway)	All inhabitants ≥ 20 y of age in 1 county invited	$n = 65\,238$ (69.8% of those invited); median age, 49 y	$n = 102$ (0.16%): 73 (0.24%) men ($n = 30\,509$); 29 (0.08%) women ($n = 34\,729$)	0.74% men; 0.36% women	ND	$n = 4$
Leggett et al., 1990 (25)	Employees (Australia)	Volunteers	$n = 1968$ (51.6% of eligible): 1043 men; 925 women	$n = 7$ (0.36%): 4 (0.38%) men (mean age, 32 y); 3 (0.32%) women (mean age, 39 y)	$n = 7$ (0.36%)	$n = 8$ (0.41%)	$n = 0$
Niederau et al., 1998 (22)	Employees (West Germany)	All new employees	$n = 3012$ (99% of eligible; mean age, NA): 2515 men; 497 women	$n = 10$ (0.33%): 9 (0.36%) men (mean age, 37.6 y); 1 (0.20%) woman (age 57 y)	$n = 29.8$ (1%): 24.3 (1%) men; 5.5 (1.1%) women	$n = 11$ (0.37%)	$n = 0$
Barton et al., 2002 (26)	Employees (Alabama)	Volunteers (employees, retirees, spouse)	$n = 2199$ (1205 employees and 994 nonemployees; mean age, 48 y): 1506 white men; 124 black men; 526 white women; 43 black women	$n = 7$ (0.32%): 7 (0.46%) white men; 0 black men, white women, or black women.	$n = 8$ (0.36%): 8 (0.53%) white men	ND	$n = 0$
McDonnell et al., 1999 (27)	Employees (Springfield, Missouri)	All employees invited	$n = 1653$ (28% of invited; mean age, 41 y): 288 men; 1365 women; 98% white	$n = 3$ (0.18%): 1 (0.35%) man (age 52 y); 2 (0.15%) women (ages 37 y and 40 y)	$n = 13$ (0.79%): 1 (0.35%) man; 12 (0.88%) women	ND	$n = 0$
Smith et al., 1997 (28)	Employees (Boston, Massachusetts)	Volunteers	$n = 2294$ (mean age, 49 y): 1859 men; 435 women; 86.1% white; 10.0% black; 3.8% other	$n = 5$ (0.22%): 5 (0.29%) men (mean age, 46.6 y); 0 women	$n = 5$ (0.22%): 5 (0.29%) men	$n = 7$ (0.31%): 7 (0.38%) men	$n = 1$
Edwards et al., 1988 (29)	Blood donors (Utah)	Healthy blood donors: sampling ND	$n = 11\,065$: 5840 men (mean age, 37.5 y); 5225 women (mean age, 34.7 y)	$n = 16$ (0.14%): 12 (0.21%) men (mean age, 28.5 y); 4 (0.01%) women (mean age, 41 y)	$n = 16$ (0.14%): 11 (0.19%) men; 5 (0.01%) women	$n = 35$ (0.32%)	NA
Benn et al., 1994 (30)	Blood donors (Germany)	ND (prospective blood donors)	$n = 1265$ (mean age, 26 y): 633 men; 632 women	$n = 3$ (0.24%): 3 (0.47%) men; 0 women	$n = 3$ (0.24%): 3 (0.47%) men	ND	ND
Wiggers et al., 1991 (31)	Blood donors (Denmark)	Consecutive blood donors	$n = 4302$: 2418 men; 1884 women	$n = 12$ (0.28%) (HIC not quantified, but these patients had $\geq 2+$ stainable iron)	$n = 10$ (0.23%): 9 (0.37%) men; 1 (0.05%) woman	$n = 14$ (0.33%): 13 (0.54%) men; 1 (0.05%) woman	$n = 0$
Velati et al., 1990 (32)	Blood donors (Italy)	ND	$n = 1301$: 976 men (age 18–65 y); 325 women (age 20–64 y)	$n = 2$ (HIC not quantified, but both men with grade IV siderosis on biopsy and phlebotomy > 6 g)	$n = 2$ (0.15%)	ND	$n = 0$
Olsson et al., 1984 (33)	Blood donors (Sweden)	ND	$n = 8750$: 3340 outpatients (not clearly primary care); 1311 donors; 4098 inpatients	$n = 3$ (0.23%) male blood donors	0.24%	ND	ND

* HH = hereditary hemochromatosis; HIC = hepatic iron concentration; NA = not applicable; ND = not determined.

† Definitive HH requires liver biopsy with HIC > 30 mmol/kg dry weight or >2000 mg of iron stores by phlebotomy.

‡ Determined by application of HH criteria to those with repeated elevations of transferrin saturation and serum ferritin levels who did not undergo liver biopsy or phlebotomy.

Table 3. Longitudinal Studies of Primary Iron Overload and Overt Hemochromatosis or Complications*

Study, Year (Reference)	Selection	Design	Outcome	Results	Methodologic or Quality Issues
Olynyk et al., 2004 (35)	Population survey and blood sampling of Brusselton, Australia, in 1981, 1994, and 1998: 12 people were identified and 10 C282Y homozygous individuals without HH were followed (4 men, 6 women)	Uncontrolled retrospective cohort	Change in TFS; change in SF level; cirrhosis	17-y follow-up; TFS > 45% in 10 of 10 patients (median increase, 42–76%); SF level normal in 4 of 10 patients, increased in 4 patients, stable in 4 patients, and decreased in 2 patients; 4 patients with SF level > 500 µg/L; 2 patients with stage III fibrosis; 1 patient with cirrhosis; 4 patients with arthritis; 2 patients with pigmentation; 1 patient with diabetes mellitus	No clear standardized or blinded assessment for clinical outcomes
Yamashita and Adams, 2003 (36)	22 asymptomatic untreated homozygous C282Y individuals identified in hemochromatosis registry (Ontario, Canada): 4 men and 18 women (age 28–76 y [median, 46 y])	Uncontrolled retrospective cohort	Change in SF level	Median follow-up, 4 y (2–23 y); 20 of 22 (91%) patients had normal SF levels at follow-up and 13 of 22 (59%) patients had decreased SF levels	No standardized follow-up: 14 of 22 patients had ≤4 y of follow-up—longer follow-up may change results; study actually evaluated relationship between genotype and biochemical iron overload
Andersen et al., 2004 (37)†	Population-based sample (n = 9714); 23 C282Y homozygous individuals (7 men and 16 women); comparison groups: other HFE genotypes	Historical cohort	Change in TFS; change in SF level; overt HH	Follow-up ≤ 25 y; TFS increased 50–70% and SF levels increased 100–500 µg/L for women (age 25–85 y); TFS increased 70–80% and SF levels decreased 800–400 µg/L for men (age 35–80 y); none developed HH; only C282Y homozygotes had mean TFS > 50%	Baseline comparability not described; equivalent intensity of follow-up not described; sampling conditions (fasting or nonfasting) not specified; no standard assessment of outcomes (liver biopsy or quantitative phlebotomy)

* HH = hereditary hemochromatosis; SF = serum ferritin; TFS = transferrin saturation.
 † See Ellervik et al. (39) for same dataset and diabetes mellitus.

creased substantially after 25 years of follow-up, but no homozygote developed hereditary hemochromatosis. In summary, these studies did not consistently identify increasing transferrin saturation and serum ferritin levels over time and did not demonstrate a clear link to the overt clinical manifestation of hereditary hemochromatosis.

Three studies examined the relationship between biochemical measures of iron overload and diabetes mellitus (Table 4). Jiang and colleagues (38) used blood samples obtained from 32 826 women in the Nurses' Health Study cohort between 1989 and 1990 who did not have diabetes mellitus, cardiovascular disease, or cancer. Multivariate relative risk increased across the quintiles of the initial ferritin levels (1.00, 1.09, 1.26, 1.30, and 2.68, respectively; $P < 0.001$ for trend). However, the results must be interpreted cautiously because cases and controls had several differences at baseline. Ellervik and colleagues (39) compared Danish patients with type 1 diabetes mellitus with controls who were selected from the Copenhagen City Heart Study. Nine patients with diabetes who were homozygous for C282Y had transferrin saturation greater than 50%, and 6

of these patients had cirrhosis by liver biopsy. Ellervik and colleagues did not directly compare transferrin saturation or serum ferritin levels between those with and without diabetes mellitus to allow a direct determination of the association, and they did not present comparison data for cases and controls. Mainous and colleagues (40) used the National Health and Nutrition Examination Survey I (NHANES I) database. The adjusted odds ratio of diabetes (controlling for age, sex, race, cholesterol level, obesity, and hypertension) was 0.89 (95% CI, 0.59 to 1.34) for transferrin saturation greater than 45%, 0.95 (CI, 0.53 to 1.70) for transferrin saturation greater than 50%, and 1.03 (CI, 0.44 to 2.43) for transferrin saturation greater than 55%. However, Mainous and colleagues did not actually identify patients with sustained elevations in transferrin saturation and serum ferritin levels and did not measure the association with diabetes mellitus.

Three studies examined the relationship between biochemical measures of iron excess and cirrhosis (Table 5). All were cross-sectional studies. Two studies (41, 42) developed a prediction rule for patients homozygous for the C282Y mutation to diagnose or exclude cirrhosis and to

more clearly define those needing liver biopsy. Both studies had separate derivation and validation populations. The earlier study (41) aimed to predict the absence of cirrhosis. It was derived in a French population and validated in a Canadian population. Only 1 of 105 patients (0.9%) with a ferritin level of 1000 $\mu\text{g/L}$ or less had cirrhosis. In combination with a normal aspartate aminotransferase (AST) level and no hepatomegaly, 0 of 94 patients had cirrhosis. Findings in the validation population were similar. The more recent follow-up report (42) found that ferritin levels greater than 1000 $\mu\text{g/L}$, platelet counts less than 200×10^9 cells/L, and elevated AST levels led to a correct diagnosis of cirrhosis in 77% of the Canadian participants and in 90% of the French participants who were tested. Morrison and colleagues (5) found that patients with ferritin levels less than 1000 $\mu\text{g/L}$ were unlikely to have cirrhosis on liver biopsy (1 of 93 patients). These 3 studies strongly suggest that patients who are at high risk for hereditary hemochromatosis (homozygous C282Y mutation) with serum ferritin levels of 1000 $\mu\text{g/L}$ or less are unlikely to have cirrhosis.

Mahon and colleagues (43) examined the relationship between C282Y mutations and idiopathic dilated cardiomyopathy (Table 6). This case-control study demonstrated that 31 of 207 cases (15%) carried the C282Y mu-

tation compared with 24 of 200 controls (12%) (adjusted odds ratio, 1.2 [CI, 0.7 to 2.2]). With respect to the H63D mutation, the odds ratio was 1.6 (CI, 1.1 to 2.5). Serum iron and transferrin saturation did not correlate with disease severity or survival. The clinical significance of the link of the H63D mutation with cardiomyopathy is unclear.

Mainous and colleagues (44) examined the association between transferrin saturation and all-cause mortality by using the NHANES I database (Table 6). After controlling for comorbid disease, smoking, and cholesterol level, all-cause mortality statistically significantly increased for transferrin saturation greater than 55% compared with those with lower transferrin saturation (hazard ratio, 1.60 [CI, 1.17 to 2.21]). Although no one who died had hereditary hemochromatosis listed as a cause of death, they were more likely to have cirrhosis or diabetes mellitus.

The Relationship between Primary Iron Tissue Deposition and Hereditary Hemochromatosis-Related Disease

We identified 13 original studies (7, 45–56) (Appendix Figure 3, available at www.annals.org). Seven studies explored the relationship of hereditary hemochromatosis

Table 4. Relationship between Primary Iron Overload Defined by Transferrin Saturation and Serum Ferritin Level and Diabetes Mellitus*

Study, Year (Reference)	Design	Selection	Definition of Primary Iron Overload	Outcome	Blinded Outcome Assessment	Results	Methodologic or Quality Issues
Jiang et al., 2004 (38)	Prospective nested case-control	698 RNs with DM (in 2000) from 32 826 women without DM in 1989–1990 (cases); 716 randomly sampled RNs without DM from 1989–2000 (controls), group-matched for age, race, and fasting status	SF levels	Association of SF with DM	Yes, for validation of cases; no, for validation of controls	Baseline mean SF level, 109 $\mu\text{g/L}$ for cases and 71.5 $\mu\text{g/L}$ for controls ($P < 0.001$); multivariate RR for patients in upper quintile of SF levels, 2.68 (95% CI, 1.75–4.11)	Cases and controls statistically significantly differed in 1989–1990 for BMI, physical activity, CRP, fasting insulin level, family history of DM, and some dietary factors suggesting lack of baseline comparability
Ellervik et al., 2001 (39)	Case-control	716 cases (90% eligible) of consecutive patients presenting to 1 DM center in Denmark; 9174 controls of representative sample of Danish population in Copenhagen City Heart Study (37); stratified by age and sex	Not clearly defined but did measure TFS, SF levels, liver histology (in some), arthritis, heart disease, and hypogonadism	Association of genotype with DM	No	OR for C282Y or C282Y individuals, 4.6 (95% CI, 2.0–10.1); of 9 homozygous patients, 9 had TFS > 50%, 5 had SF levels > 1000 $\mu\text{g/L}$, 6 had cirrhosis, 1 had arthritis, 1 had heart disease, and 4 were hypogonadal	Data for TFS and SF levels in controls were not presented; no baseline comparison data for cases and controls; no standardized clinical assessment of controls; no blinded assessments
Mainous et al., 2002 (40)	Retrospective cohort	NHANES I (1971–1975) study with 9274 participants 25–74 y of age initially without DM; incidence of DM, 10.2%	TFS at following cut-off values: >45%, >50%, >55%, >60%, >62%	Self-reported DM	No	TFS > 55% for 7.5% of patients with DM compared with TFS \leq 45% for 10.2% of patients with DM ($P = 0.38$); baseline comparison data not presented	Equivalent baseline susceptibility for DM not demonstrated; no validation of DM in those with and without DM

* BMI = body mass index; CRP = C-reactive protein; DM = diabetes mellitus; CHF = congestive heart failure; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; RN = registered nurse; RR = relative risk; SF = serum ferritin; TFS = transferrin saturation.

Table 5. Relationship between Primary Iron Overload Defined by Transferrin Saturation or Serum Ferritin Level and Cirrhosis*

Study, Year (Reference)	Design	Patient Selection	Definition of Primary Iron Overload	Outcome	Blinded Assessment	Results	Methodologic or Quality Issues
Guyader et al., 1998 (41)	Cross-sectional to develop prediction rule	Training set: French database of 197 HFE-genotyped patients Validation set: 113 Canadian patients homozygous for C282Y	TFS \leq 45%; SF level \leq 400 μ g/L were defined as normal; evaluated several cut-off values for abnormal results	Liver fibrosis (grade 3 or 4)	Pathologists were blinded to clinical information in both France and Canada	Training set: 52 of 197 patients had fibrosis; 1 of 105 patients with SF levels \leq 1000 μ g/L had fibrosis (none with normal AST level or hepatomegaly) Validation set: 28 of 113 patients had fibrosis; 2 of 60 with SF levels \leq 1000 μ g/L had fibrosis; 0 of 51 with SF levels \leq 1000 μ g/L, normal AST levels, and no hepatomegaly had cirrhosis	Patient spectrum: Only 66% of French patients were asymptomatic at time of identification; not reflective of primary care setting
Beaton et al., 2002 (42)	Cross-sectional to develop prediction rule	Training set: Canadian database of 193 homozygous C282Y patients (113 were included in Guyader et al. [41]) Validation set: 162 French patients homozygous for C282Y	TFS; SF level	Cirrhosis	Not stated	Training set: 27 of 193 patients had cirrhosis; 0 of 118 patients with SF levels $<$ 1000 μ g/L had cirrhosis; 17 of 22 patients with SF levels $>$ 1000 μ g/L, increased AST level, and platelet count $<$ 200×10^9 cells/L had cirrhosis Validation set: 25 of 162 patients had cirrhosis; 0 of 99 patients with SF levels $<$ 1000 μ g/L had cirrhosis; 9 of 10 patients with SF levels $>$ 1000 μ g/L, increased AST levels, and platelet count $<$ 200×10^9 cells/L had cirrhosis	Patient spectrum: 58% presented with clinical symptoms or iron overload or increases in iron indices; not reflective of primary care setting
Morrison et al., 2003 (5)	Cross-sectional	182 patients with HH identified by record review at 6 tertiary facilities; no other active liver disease or evidence of alcohol abuse	HIC or HII or removal of $>$ 4 g by phlebotomy; SF level	Cirrhosis	Two investigators blinded to laboratory and clinical data reviewed pathology reports	40 of 182 patients had cirrhosis; 1 of 93 patients with SF level $<$ 1000 μ g/L had cirrhosis	Patient spectrum: comorbid features not presented; not reflective of primary care setting

* AST = aspartate aminotransferase; HH = hereditary hemochromatosis; HIC = hepatic iron concentration; HII = hepatic iron index; SF = serum ferritin; TFS = transferrin saturation.

and survival, and the remainder evaluated the association of this disease with other complications (Table 7).

Wojcik and colleagues (45), studying patients from a tertiary care facility, found that actuarial survival at 5, 10, and 20 years was 95%, 93%, and 66%, respectively, with a mean follow-up of 7.3 years. At the time of diagnosis, 36% of men and 19% of women had life-threatening diseases. Cirrhosis and diabetes mellitus were the only major factors that affected survival. Milman and colleagues (46) found that after a median of 8.5 years, survival in patients with

cirrhosis and diabetes was statistically significantly lower than survival in those without either complication (who had a survival similar to that in the general population on the basis of a nonconcurrent, historical control). The main causes of death were liver failure secondary to cirrhosis and cirrhosis with liver cancer. Although not clearly stated, Niederau and colleagues' studies (7, 56) probably shared some of the same patients. Their more recent publication (7) also found that survival in noncirrhotic and nondiabetic patients with hereditary hemochromatosis was similar

to survival in those in the healthy population (nonconcurrent, historical control). The adjusted relative risk for death for cirrhosis and diabetes mellitus was 4.3 and 2.4, respectively. Fargion and colleagues (47) found that over a median of 44 months, 44 of 146 patients with cirrhosis died (20 with hepatocellular carcinoma and 10 with liver failure). No deaths occurred in patients without cirrhosis. Adams and colleagues (48) found that patients with hereditary hemochromatosis and cirrhosis were 5.5 times more likely to die than those without cirrhosis. Diabetes mellitus did not increase the risk. Yang and colleagues (49) conducted a retrospective analysis of the Multiple-Cause Mortality Files compiled by the National Center for Health Statistics. Patients who died of hereditary hemochromatosis were more likely to have liver neoplasms, liver disease, and cardiomyopathy. Conversely, patients who died of liver neoplasms, liver disease, and cardiomyopathy were more likely to have hereditary hemochromatosis than those without these conditions. These studies consistently demonstrated a link between hereditary hemochromatosis-associated cirrhosis and reduced survival and strongly suggest a link between hereditary hemochromatosis-related diabetes mellitus and reduced survival.

Adams (50), using receiver-operating characteristic curve analysis to identify the threshold of hepatic iron concentration for predicting the presence of cirrhosis, derived an optimal threshold of 283 mmol/kg dry weight, with a sensitivity of 85% and a specificity of 84%. Fargion and colleagues (51) evaluated the prognostic factors for hepatocellular carcinoma in hereditary hemochromatosis. Hepatocellular carcinoma developed in 29% of patients with cirrhosis compared with 0% in those without cirrhosis. The 2 studies by Deugnier and colleagues (52, 53) identified a specific preneoplastic change (iron-free foci) in patients with hereditary hemochromatosis that was associated with the development of hepatocellular carcinoma. Ammann and colleagues (54) found that out of 36 patients

with hereditary hemochromatosis, 5 cases of hepatoma and 6 cases of extrahepatic carcinoma developed over 8 years.

The case-control study by Salonen and colleagues (55) found that men with high iron stores were 2.4 times more likely to have diabetes than men with lower iron stores.

Subquestion 3: How Diagnostically Useful Are Transferrin Saturation and Serum Ferritin Level in Identifying Primary Care Patients with Hereditary Hemochromatosis?

We identified 3 studies (20–22) conducted in the primary care setting (Appendix Figure 4, available at www.annals.org). No study independently and blindly compared the screening tests for iron overload (transferrin saturation and serum ferritin level) with the gold standard (liver biopsy or mobilizable iron by phlebotomy) in all screened patients.

Phatak and colleagues (21) screened for sustained transferrin saturation of 45% or greater ($n = 311$). Of 50 patients with transferrin saturation greater than 55% and serum ferritin levels greater than 200 $\mu\text{g/L}$, 35 patients were offered liver biopsy and 21 patients underwent the procedure. Eighteen patients (86%) were found to have hereditary hemochromatosis. Of 29 patients who declined or were not offered liver biopsy, 17 patients were labeled as having clinically proven hereditary hemochromatosis. Of this group, only 2 patients had mobilizable iron stores of 2 g or more. Using the strict HEIRS study criteria and these diagnostic cutoff levels, we identified hereditary hemochromatosis in 20 patients (40%). Using the authors' criteria, 36 patients (72%) had hereditary hemochromatosis. For those with transferrin saturation between 45% and 55% and serum ferritin levels greater than 200 $\mu\text{g/L}$ ($n = 78$), biopsy was recommended in 13 patients and hereditary hemochromatosis was identified in 7 patients. Of those who did not have a recommendation for biopsy ($n = 65$),

Table 6. Relationship between Primary Iron Overload Defined by Transferrin Saturation or Serum Ferritin Level and Cardiomyopathy or Mortality*

Study, Year (Reference)	Design	Patient Selection	Definition of Primary Iron Overload	Outcome	Blinded Assessment	Results	Methodologic or Quality Issues
Mahon et al., 2000 (43)	Case-control	Patients attending cardiomyopathy clinic at a tertiary referral center: 207 white case-patients with DCM and 200 controls	C282Y and H63D genotypes; TFS	DCM; survival	Unknown	TFS not associated with reduced survival; H63D increased in patients with idiopathic DCM	Patient spectrum
Mainous et al., 2004 (44)	Retrospective cohort	NHANES I (1971–1975) and NHEFS: 10 714 people age 25–74 y with baseline and follow-up data	TFS cut-off values: >45%, >50%, >55%, >60%	All-cause mortality	No	TFS > 55% (HR, 1.60 [95% CI, 1.17–2.21]); cause of death, 6.7% with cirrhosis and 6.0% with DM	Authors attempted to control for age, sex, poverty, education, total cholesterol level, smoking, and comorbid conditions

* DCM = dilated cardiomyopathy; DM = diabetes mellitus; HR = hazard ratio; NHANES = National Health and Nutritional Examination Survey; NHEFS = NHANES I Epidemiologic Follow-up Study; TFS = transferrin saturation.

Table 7. Relationship between Primary Iron Overload Defined by Tissue Iron Deposition and Complications*

Study, Year (Reference)	Design	Patient Selection	Definition of Primary Iron Overload	Outcome	Blinded Assessment	Results	Methodologic or Quality Issues
Wojcik et al., 2002 (45)	Retrospective cohort	All C282Y homozygous patients (n = 277) referred to a tertiary HH center and 16 C282Y homozygous patients from population-based study	Hepatic iron	Survival	No	Life-threatening diseases (cirrhosis, HCC, DM, and heart disease) were present in 36% of men and 19% women referred; 95%, 93%, and 66% survived at 5, 10, and 20 y of follow-up, respectively; cirrhosis and DM associated with reduced survival	Referral bias—patients referred had more advanced disease with many patients having complications of HH
Milman et al., 2001 (46)	Retrospective cohort	179 Danish patients with overt HH from death registry, patient registry, and queries to medicine departments	Hepatic iron in 162 patients	Survival in those with or without cirrhosis or those with or without DM	No	Median follow-up of 8.5 y for a cohort of 158 patients (those living when identified for study), of whom 128 had cirrhosis and 57 had DM; survival decreased for entire cohort compared with population cohort	
Niederer et al., 1996 (7)	Prospective cohort	251 patients with overt HH; those without cirrhosis (n = 109) were compared with those with cirrhosis (n = 142)	Hepatic iron	Survival; HCC; cardiomyopathy; cirrhosis; DM	No	Median follow-up of 14.6 years; decreased survival in those with cirrhosis; decreased survival in those with DM; adjusted RR for death for cirrhosis and diabetes mellitus was 4.3 and 2.4, respectively; no difference in survival with arthropathy; cumulative survival at 5, 10, 15, 20, 25, and 30 y was 93%, 77%, 62%, 55%, 46%, and 20%, respectively; phlebotomy treatment improved degree of fibrosis in 42 patients, worsened in 2 patients, and did not change in 141 patients	Baseline comparability not demonstrated (cirrhotic and noncirrhotic patients differed for several variables)
Fargion et al., 1992 (47)	Prospective cohort	212 consecutive Italian patients with HH	Hepatic iron	Survival; cirrhosis	No	Median follow-up of 44 mo; decreased survival in those with cirrhosis (n = 146); of 44 deaths in cirrhotic patients, 20 died of HCC, 10 died of liver failure, 3 died of CHF, 6 died of extrahepatic cancer, and 5 died from causes unrelated to hemochromatosis; of cirrhotic patients, 65% had SF levels > 3 times the upper limit of normal and 88% had grade IV Peris stain	Baseline comparability not established for age, alcohol, anti-HCV-positivity, and clinical factors
Adams et al., 1991 (48)	Retrospective cohort	85 patients at a Canadian medical center who received their diagnosis between 1958 and 1989	Liver biopsy in all patients	Observed survival in those with and without cirrhosis or DM compared with expected survival	Classification of liver biopsy specimens (normal, fibrotic, or cirrhotic) without knowledge of clinical outcomes	Mean (SD) follow-up of 8 y (6.8 y); 17 deaths; adjusted RR for death for cirrhosis was 5.5; no increased risk with DM	Comparisons to nonconcurrent theoretical cohort; baseline equivalence between those with and without complications not demonstrated
Yang et al., 1998 (49)	Retrospective cross-sectional review of mortality from the Multiple-Cause Mortality Files compiled by the National Center for Health Statistics	4858 HH deaths between 1979 and 1992	Death certificates	Calculated age-adjusted and age-specific mortality rates; liver neoplasms; liver disease; cardiomyopathy	No	60% increase in listing HH as cause of death from 1979 to 1992; HH deaths were 23, 13, and 5 times more likely to have liver neoplasms, liver disease, and cardiomyopathy, respectively; HH was 83 times more likely in those with liver neoplasms and diabetes than in those without these combinations	Death certificate diagnosis without primary data verification; no blinded assessment
Adams, 2001 (50)	Cross-sectional	100 C282Y homozygous individuals who had a liver biopsy with HIC determinations	Hepatic iron	HIC threshold for predicting cirrhosis	No	Optimal HIC threshold (ROC curve analysis), 283 mmol/kg dry weight; sensitivity, 85%; specificity, 84%	No blinded independent comparison of HIC to presence or absence of cirrhosis
Fargion et al., 1994 (51)	Prospective cohort	152 patients with HH; most patients (69%) referred for evaluation and 97 patients had cirrhosis	Liver biopsy in 135 patients and therapeutic phlebotomy in 17 patients	HCC	No	HCC: 28 of 97 patients with cirrhosis vs. 0 of 55 patients without cirrhosis; HIRs were 13.3, 4.9, 2.3, and 150.0 for age > 55 y, HBsAg, alcohol use, and all 3 factors, respectively	No blind independent assessment of HCC and clinical prediction variables
Deugnier et al., 1993 (52)	Retrospective cohort	185 French and Australian patients with HH and 14 patients with hepatic IFF were compared with 24 IFF-negative controls with HH	Hepatic iron and removable iron	Hepatocellular carcinoma	No	50% of patients with IFF had HCC vs. 8% of patients without IFF	Those with and without IFF were matched at baseline for age, sex, HIC, histologic iron grading, removable iron, and duration of follow-up, but baseline equivalence is unknown
Deugnier et al., 1993 (53)	Case-control	54 case-patients with primary liver cancer and HH at 2 centers and 50 control patients with HH and no primary liver cancer	Hepatic iron	Primary liver cancer and association with cirrhosis and iron	No	22 cases had undiagnosed HH at time of cancer diagnosis; 34 of 42 (81%) cases had cirrhosis vs. 11 of 39 (26%) controls (P < 0.001); 26 of 54 cases (48%) had alcoholism vs. 12 of 47 (25%) controls (P < 0.03); 50% of cases smoked vs. 18% of controls	Cases and controls matched for sex, age at HH diagnosis, follow-up duration, and HIC or removable iron; however, baseline equivalence unknown

Table 7—Continued

Study, Year (Reference)	Design	Patient Selection	Definition of Primary Iron Overload	Outcome	Blinded Assessment	Results	Methodologic or Quality Issues
Ammann et al., 1980 (54)	Retrospective uncontrolled cohort	36 consecutive patients with HH	Hepatic iron	Hepatocellular carcinoma and extrahepatic carcinoma	No	Mean follow-up, 8 y; 10 patients developed 11 types of carcinoma: 5 cases of hepatomas, 4 cases of lung cancer, 1 case of oral cavity, 1 case of thyroid cancer	No comparison group to control for other cancer risks
Salonen et al., 1998 (55)	Case-control	41 cases of 1038 Finnish men who developed new DM over 4 y and 82 controls (men) matched for age, time of examination, residence, smoking, and other characteristics	Ratio of transferrin receptors to ferritin	DM	No	Those in highest quartile of iron stores compared with those in lowest: OR, 2.40 (95% CI, 1.03–5.50)	No baseline data to ensure comparability of cases and controls; sampling of controls not defined; TFS and SF levels between groups were not presented

* CHF = congestive heart failure; DM = diabetes mellitus; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HH = hereditary hemochromatosis; HIC = hepatic iron concentration; HR = hazard ratio; IFF = iron-free foci; OR = odds ratio; ROC = receiver-operating characteristic; RR = relative risk; SF = serum ferritin; TFS = transferrin saturation.

2 patients had mobilizable iron stores of 2 g or more. Using strict criteria and these cutoff levels, 9 of 78 screened patients (11.5%) had hereditary hemochromatosis. Using the authors' criteria, we identified hereditary hemochromatosis in 11 patients (14%).

Niederau and colleagues (22) studied 3027 healthy outpatients in West Germany. They used thresholds of transferrin saturation greater than 50% in men and greater than 60% in women and serum ferritin levels of 250 $\mu\text{g/L}$ in men and 350 $\mu\text{g/L}$ in women. Using these cutoff levels, 235 patients (7.8%) had elevated serum ferritin levels, 139 patients (4.6%) had elevated transferrin saturation, and 44 patients (1.5%) had both. Of this latter group who were retested, 31 patients (1% of total) had persistently elevated transferrin saturation and serum ferritin levels. Twenty-three patients continued with further evaluation. We identified hereditary hemochromatosis in 18 patients (78%) by using these diagnostic cutoff levels for transferrin saturation and serum ferritin levels.

Baer and colleagues (20) studied 3977 consecutive men 30 years of age or older who belonged to the Oakland Kaiser Permanente health maintenance organization. Those with transferrin saturation of 62% or greater underwent repeated testing in the fasting state. Patients with persistently elevated transferrin saturation ($\geq 62\%$) and serum ferritin levels of 500 $\mu\text{g/L}$ or greater were offered a liver biopsy. Forty patients (1%) had transferrin saturation that exceeded the cutoff value. Thirty-six patients were available for follow-up. Of these, 14 patients with persistent elevations were referred for liver biopsy and 12 patients underwent the procedure. One of the 12 patients had a serum ferritin level less than 500 $\mu\text{g/L}$. These 12 patients had hereditary hemochromatosis defined by strict criteria. All patients with transferrin saturation of 62% or greater and serum ferritin levels of 500 $\mu\text{g/L}$ or greater had hereditary hemochromatosis.

These 3 studies demonstrate substantial variation in the testing sequence; the decision thresholds for transferrin

saturation, serum ferritin level, and their combined results; and the application of the gold standard. Patients with levels less than the threshold values at any location in the testing sequence were not assessed by the gold standard or followed for the development of disease. Not all patients with levels greater than the threshold values underwent the gold standard assessment. Consequently, sensitivity and specificity cannot be determined. The proportion of patients with levels greater than the threshold values who underwent the gold standard assessment does provide a limited estimate of the positive predictive value.

Other researchers have reviewed the proportion of screened patients in a general population with initial and repeatedly positive transferrin saturation test results (57). Initial positive test results were found in 1.1% to 6.2% of patients screened. A relationship between the proportion positive and the diagnostic cutoff level was not apparent. The highest proportion was in blood donors with transferrin saturation cutoff values of 50% or greater (29), and the lowest proportion was in those with cutoff values of 55% or greater (28). This differs from the 3 primary care studies in which the more stringent criteria were associated with a higher proportion of patients identified with hereditary hemochromatosis.

Subquestion 4: Is Phlebotomy Efficacious in Reducing Morbid or Fatal Complications in Asymptomatic Patients with Hereditary Hemochromatosis?

We did not identify any randomized trial. We identified only 1 study for inclusion because it compared patients who were adequately phlebotomized with those who were not adequately phlebotomized (46). We identified an additional study (7) by manual search because of its before-after phlebotomy comparison of liver histology (Appendix Figure 5, available at www.annals.org).

Milman and colleagues (46) retrospectively identified a cohort of 158 patients with hereditary hemochromatosis by querying departments of medicine and pediatrics in

Denmark and by reviewing a Danish death registry. Patients were followed for a median period of 8.5 years. Survival of patients who were adequately phlebotomized ($n = 66$) was greater than survival of those who were not adequately phlebotomized ($n = 62$). The estimated Kaplan–Meier survival was 93% versus 48% at 5 years and 78% versus 32% at 10 years. Furthermore, adequately treated patients with cirrhosis or diabetes had better survival than those who were not adequately treated. However, we could not determine the clinical comparability of patients with cirrhosis who were or were not adequately treated.

Niederau and colleagues (7) studied a cohort of 251 German patients with hereditary hemochromatosis for a mean follow-up of 14.1 years. Patients underwent an initial liver biopsy and were then phlebotomized until serum ferritin level was normalized. At this point, they underwent a second biopsy. A before–after phlebotomy comparison was performed in 185 patients. However, no methodologic safeguards minimized ascertainment bias. Forty-two patients had improved liver histology after phlebotomy, and 2 patients had deterioration in histology. Improvement or deterioration was based on changes in fibrosis stage. Except for 1 patient, all improvements were by 1 stage. One patient had a 2-stage improvement. The 2 patients who deteriorated had a 1-stage decrement. The remaining 141 patients did not change. However, given the possibility of sampling error from one liver biopsy to the next, any change in histologic status must be interpreted cautiously.

No studies met a standard of evidence (blinded, randomized, controlled trial) that clearly establishes the efficacy of therapeutic phlebotomy. However, they do support the existing model of disease and suggest a benefit. Given the current opinion and the lack of clinically significant side effects, a randomized, controlled trial will probably not be performed.

Subquestion 5: Do the Benefits Outweigh the Risks in Screening Primary Care Patients for Hereditary Hemochromatosis?

Without the ability to establish the efficacy of therapeutic phlebotomy in a research setting, we could not establish the effectiveness of a screening approach directly in the primary care setting. The electronic literature search for a decision-analytic model of a cost-effectiveness analysis identified 4 relevant postings. Two models (58, 59) were previously reviewed in *Annals of Internal Medicine* (13). Cogswell and colleagues (13) identified the major determinants of screening cost-effectiveness: prevalence and disease burden; sensitivity and specificity of the screening tests; adherence to screening, diagnosis, and therapy; and costs of screening, diagnosis, and therapy. The lack of data on natural history led decision analysts to use data from hospital registries of patients affected with hemochromatosis, increasing the possibility of overestimation of morbidity and mortality.

Two studies (60, 61) have been published since Cog-

swell and colleagues' comprehensive review, and we evaluated them for new insights. In their decision-analytic model, Asberg and colleagues (60) based the prevalence of hereditary hemochromatosis and the risk for liver cirrhosis on cross-sectional data obtained from a population of 30 509 men (24). If their model accurately reflects reality, phenotypic screening of a cohort of 10 000 young (30 years of age), predominantly white men from the general population would generate a gain of 8 quality-adjusted life-years compared with waiting for symptomatic disease to occur. They estimated the costs to be \$250 per quality-adjusted life-year saved.

The model used a screening approach that began with an initial nonfasting transferrin saturation (cutoff level, >55%), followed by a fasting transferrin saturation if the first result was positive. If this second test result was greater than 55%, they measured the serum ferritin level. If the serum ferritin level was elevated (>200 $\mu\text{mol/L}$), they referred the patient for clinical examination. They did not base the diagnosis of hereditary hemochromatosis on invasive liver biopsy results or the amount of mobilizable iron removed. Therefore, they did not assign risk to the clinical examination. If they could not identify a secondary cause of iron overload, they labeled the patients as having hereditary hemochromatosis. Consequently, they actually incorporated the screening tests into the gold standard of diagnosis, which explain the high estimated sensitivity and specificity of the screening tests used in their model. In their theoretical cohort of 10 000 men, Asberg and colleagues estimate that 53 people with hereditary hemochromatosis would be identified. However, if we take the available data from primary care (21) and use a strict case definition (biopsy or mobilizable iron), we estimate that only 18 patients with hereditary hemochromatosis would be identified. These marked differences illustrate the effect of differing case definitions on the models.

Furthermore, Asberg and colleagues (60) used Markov models to estimate outcomes for men with hereditary hemochromatosis with or without treatment (phlebotomy) and men without hereditary hemochromatosis with or without phlebotomy (4 health states). The only complication of hereditary hemochromatosis used to model survival was the presence or absence of cirrhosis. They estimated the incidence of cirrhosis from cross-sectional data of men with cirrhosis at the time of initial diagnosis across various age groups in 2 studies (21, 24). Asberg and colleagues assumed that men with hereditary hemochromatosis but without cirrhosis at diagnosis and treated with phlebotomy would not develop cirrhosis and estimated their quality of life to be 1.0. However, the only available data on the before–after phlebotomy effect on liver histology suggest that 77% of patients had no change during the before–after time period (from initial diagnosis to normalization of serum ferritin level) and 1% progressed (7). Although presumed to be true, on the basis of this information, whether phlebotomy will prevent the development of cirrhosis in all

treated patients over longer periods of time is not certain. Furthermore, Asberg and colleagues did not consider the effect of being labeled with hereditary hemochromatosis (psychologically or economically).

The study by Adams and Valberg (61) suggested that screening blood donors for hereditary hemochromatosis may save money. They used a decision tree for the natural history of unscreened donors that was similar to their previous cost models (62, 63). The target population for this decision analysis was a hypothetical cohort of 10 000 voluntary blood donors and 50 siblings of identified homozygotes. They compared genotypic screening with phenotypic screening and modeled the effect of diabetes mellitus and heart failure on outcomes, as well as cirrhosis. As in previous analyses, they used a database of 170 homozygous patients with hereditary hemochromatosis who were referred to a tertiary care facility. An optimal screening strategy used phenotypic testing followed by genotyping—unless the cost of genetic testing was less than \$28.

Unfortunately, these 2 new analyses are still subject to the limitations that we have noted in the primary studies. The lack of data on natural history has forced analysts to rely on cross-sectional studies or databases at large tertiary care referral sites. More recent data have raised additional questions about the usefulness of genetic testing because many people with *HFE* mutations do not progress to overt disease, and we have no prospective data on the incidence of cirrhosis or diabetes mellitus in patients with elevations of transferrin saturation and serum ferritin levels but without disease at the time of diagnosis.

DISCUSSION

On the basis of our review of the literature, hereditary hemochromatosis is a common genetic disease within the primary care setting, especially in white men older than 40 years of age. Given the relatively high estimated prevalence of hereditary hemochromatosis (1 in 127 patients to 1 in 270 patients), we must understand the magnitude of the burden that will likely occur. Ideally, the answer would come from a large prospective cohort study identifying patients with and without hereditary hemochromatosis at an early and uniform point in time (sustained elevations of transferrin saturation and serum ferritin levels without clinically significant liver iron deposition) and followed at regular intervals with blinded assessment to detect the important outcomes of cirrhosis, hepatocellular carcinoma, diabetes mellitus, congestive heart failure, arthritis, and death. Unfortunately, no prospective cohort studies early in the course of the disease are available to provide this information. The available data demonstrate low penetrance of *HFE* mutations and suggest that the magnitude of burden may be less than commonly believed. Specifically, 3 small longitudinal studies (34–37) of patients homozygous for the C282Y mutation did not demonstrate

predictable progression to overt clinical hereditary hemochromatosis over long periods of follow-up.

The association between phenotypic measures of iron overload (transferrin saturation and ferritin levels) and the development of iron-related complications is inconsistent. No prospective cohort studies of patients without diabetes mellitus at baseline with and without elevated biochemical measures of iron are available to determine differences in the incidence of new disease. The available retrospective studies did not ensure balanced comparison groups, making selection bias likely (38–40). Consequently, the interpretation of an association between serum iron measures and diabetes mellitus was difficult at best. The prospective studies of patients with hereditary hemochromatosis based on liver iron deposition demonstrated a high prevalence of co-existing diabetes mellitus, and diabetes mellitus was independently associated with an increased risk for death in many of these cohorts. Given its high prevalence in patients with overt hereditary hemochromatosis, diabetes mellitus is probably associated, but the magnitude of risk is not clear. Associations with arthritis and congestive heart failure were not well supported.

The strongest link between iron overload and disease is the association of serum ferritin levels with cirrhosis. Two separate research groups consistently demonstrated the usefulness of the test for identifying a low-risk group for the presence of cirrhosis (serum ferritin level < 1000 $\mu\text{g/L}$). In addition, a prediction rule for the presence of cirrhosis has been developed and validated. Serum ferritin level is useful for predicting the prevalence of cirrhosis at a single point in time. A patient with a serum ferritin level less than 1000 $\mu\text{g/L}$ without hepatomegaly and a normal AST level is unlikely to have cirrhosis. On the other hand, patients with serum ferritin levels greater than 1000 $\mu\text{g/L}$, platelet counts less than 200×10^9 cells/L, and elevated AST levels have a high probability of cirrhosis. The available literature suggest that the presence of cirrhosis in patients with hereditary hemochromatosis at the time of diagnosis portends a poor prognosis (a substantial reduction in survival and an increased risk for hepatocellular carcinoma). Only 5% of those with hereditary hemochromatosis identified by screening in a primary care setting had cirrhosis. However, the available data did not permit determination of the incidence of new cases of cirrhosis in patients with hepatic iron deposition at the time of original diagnosis.

The identification of the *HFE* gene and development of a genetic test to detect the presence of C282Y mutation has made the case definition of hereditary hemochromatosis vary (9). This has resulted in several different approaches for studying the diagnostic efficacy of available tests. Some investigators used genotyping as the gold standard and determined the sensitivity and specificity of phenotypic tests in predicting the presence or absence of homozygous C282Y genotypes. Without convincing data to demonstrate that patients with *HFE* mutations will progress to disease or early death, this definition may not

have clinical utility. Other investigators have used persistently elevated transferrin saturation and serum ferritin levels, without biopsy or quantitative phlebotomy, to diagnose hereditary hemochromatosis. This results in a diagnostic incorporation bias (19). Consequently, we selected a gold standard for hereditary hemochromatosis for our review that required independent demonstration of iron overload (liver deposition or the amount of iron removed by phlebotomy). The use of this case definition limits the ability to determine the diagnostic efficacy of phenotypic tests in the primary care setting because patients with transferrin saturation or a second serum ferritin level interpreted as normal do not undergo liver biopsy, and no prospective follow-up data are available for those with negative test results to identify false-negative results. Further, only those with sustained elevations of transferrin saturation and serum ferritin levels are offered the gold standard test. Given these difficulties, determining the likelihood of disease in those with positive test results defined as sustained elevations of phenotypic measures (positive predictive value) was the best existing measure available. The diagnostic cutoff levels for transferrin saturation and serum ferritin have varied across studies as well. The higher cutoff levels (transferrin saturation $\geq 62\%$ and serum ferritin levels $\geq 500 \mu\text{g/L}$) identified a subgroup in which all patients had hereditary hemochromatosis. The least stringent criteria (transferrin saturation $\geq 45\%$ and serum ferritin levels $> 200 \mu\text{g/L}$) identified a group in which only 11.5% had hereditary hemochromatosis. Given the predictive usefulness of serum ferritin level ($<1000 \mu\text{g/L}$) for excluding the presence of cirrhosis and the high prevalence of hereditary hemochromatosis in patients screened with higher cutoff levels, using these cutoff levels in a screening program is not unreasonable. However, some patients with hereditary hemochromatosis probably would be missed, and no data on the use of repeated tests or an appropriate interval for repeated testing are available. More important, no data are available on the incidence of cirrhosis in patients with levels greater than these cutoff values and without cirrhosis at the time of hereditary hemochromatosis diagnosis.

Much remains unknown about the natural history of hereditary hemochromatosis. Although white men older than 40 years of age screened by phenotypic tests have the highest prevalence of hereditary hemochromatosis (established by liver biopsy or mobilized iron) in a primary care setting, how many without cirrhosis or other organ involvement at the time of diagnosis will progress to overt disease remains unclear. Further, no clearly defined patient or laboratory characteristics are available to risk-stratify patients into groups that are more or less likely to develop overt disease. The recent attempts to model benefits and risks of screening were not based on natural history studies and did not consider the effect of disease labeling (including insurance and social and psychological well-being).

McDonnell and Parrish (64) have reviewed and integrated the available data into a model of natural history to

estimate progression to overt disease. They estimate that, in screening a theoretical cohort of 1 million people from the general population with either phenotypic or genotypic tests, only 2 per 1 million persons screened by *HFE* screening and 3 per 1 million persons screened by transferrin saturation screening would be identified with cirrhosis. Given the potential social, psychological, and financial harms from early hereditary hemochromatosis diagnosis of an asymptomatic patient, the benefit of early diagnosis relative to the risk remains unclear. Our knowledge deficit about natural history remains an important limitation to recommendations about screening patients in primary care or the general population. The HEIRS study (34) is currently being conducted and may help to shed light on some of these issues. This primary care-based study of 100 000 adults over 5 years will provide valuable information related to the prevalence of hereditary hemochromatosis, value of phenotypic and genotypic screening tests, and benefits and risks for primary care-based screening. The results of the screening stage have been recently reported (65). The prevalence of the C282Y mutation was more common (0.44%) in non-Hispanic white persons than in other groups. For those C282Y homozygous individuals, the serum ferritin levels were elevated in 88% of men and 57% of women. However, the actual prevalence of hereditary hemochromatosis based on liver biopsy or therapeutic phlebotomy was not presented.

Hereditary hemochromatosis seems to be relatively common in certain ethnic, sex, and age groups. In patients with overt clinical manifestations, hereditary hemochromatosis can shorten survival and substantially reduce the quality of life. Our current lack of information on natural history severely limits our understanding about the burden related to this disease from a societal perspective. Phenotypic tests can identify subgroups of patients with differing probabilities of hereditary hemochromatosis by liver biopsy and can be used to predict the presence or absence of cirrhosis. No data based on randomized trials indicated the true efficacy of phlebotomy. The limited quality of the evidence base precludes phenotypic testing for a judgment that hereditary hemochromatosis in the primary care setting fulfills the necessary criteria for a screening test (16).

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APPENDIX: SEARCH METHODS AND ARTICLE SELECTION

Subquestion 1: What Is the Prevalence of Hereditary Hemochromatosis in the Primary Care Setting?

We searched the medical literature to determine the prevalence of asymptomatic hereditary hemochromatosis in primary care settings or in the general population defined by increased hepatic iron concentration on liver biopsy or by evidence of substantial iron overload on the basis of the response to therapeutic phlebotomy. We used the current and ongoing HEIRS study (34) definitions for primary iron overload (hepatic iron concentration > 30 mmol/kg dry weight or by removal of >2000 mg of storage iron by phlebotomy to achieve a serum ferritin level < 200 µg/L). We considered only individuals with evidence of phenotypic primary iron overload to have hereditary hemochromatosis. We conducted a MEDLINE search using the terms *hereditary hemochromatosis*, *hemochromatosis*, *prevalence*, *primary care*, *general population*, and *screening*. We restricted the review to original studies with at least 1000 patients. For a study to be included, the patients identified as having primary iron overload by screening (transferrin saturation and serum ferritin level) must have had either a liver biopsy or a measured response to therapeutic phlebotomy. Because many study participants with elevated transferrin saturation and serum ferritin levels declined liver biopsy or therapeutic phlebotomy, we calculated “ceiling estimates” of prevalence, assuming the same probability of primary iron overload as in those who were actually evaluated. Consequently, we presented prevalence data in 3 ways: use of the strict definition recommended in the HEIRS study, use of the reported prevalence by the investigator, and use of a ceiling estimate.

An electronic search of PubMed identified 345 unique postings through 3 March 2004. After reviewing titles and abstracts and manually reviewing references, we considered 15 studies (20–33, 66) for inclusion (Appendix Figure 1). Four studies (20–22, 66) were conducted in an outpatient clinical care setting. However, we excluded 1 of these studies (66) because it probably included inpatients and outpatient specialty clinics. The other 3 studies were conducted in a primary care setting. Two studies (23, 24) screened patients in the general population, 5 studies (22, 25–28) screened employees, and 5 studies (29–33) screened blood donors.

Subquestion 2: In Asymptomatic Patients with Hereditary Hemochromatosis, What Is the Risk for Developing Morbid Complications or for Death?

In 1998, the need for information on the natural history of hereditary hemochromatosis at various stages of iron overload was identified (18). By using the PubMed Clinical Queries filters for prognosis and the terms *hereditary hemochromatosis*, *hemochromatosis*, *transferrin saturation*, *serum ferritin*, *cirrhosis*, *hepatocellular carcinoma*, *diabetes mellitus*, *congestive heart failure*, *arthritis*, and *natural history*, we examined the literature for new evidence on the transition from states of asymptomatic iron overload (by elevated transferrin saturation and serum ferritin level) to tissue iron deposition (by liver biopsy), clinical disease, and death. We looked for prospective studies that allowed us to determine the incidence of new complications or comparative studies (retrospective or prospective cohort and case-control) that allowed us to determine the association of iron overload with the risk for complications (by relative risk or odds ratio). For a study to be included, patients had to be identified as having primary iron overload with repeated elevations of both transferrin saturation and serum ferritin levels. We determined the outcome of diabetes mellitus by using the Diabetes Expert Committee criteria (67). The outcomes of cirrhosis and hepatocellular carcinoma required tissue confirmation. The outcome of congestive heart failure required symptoms, signs, and objective assessments of reduced left ventricular systolic function (left ventricular ejection fraction 0.45). Arthritis required clinical assessment of signs and symptoms and at least evidence of synovial swelling.

Regarding the relationship between transferrin saturation–serum ferritin level and hereditary hemochromatosis–related disease, an electronic search through 20 April 2004 identified 170 unique postings. After reviewing the titles and abstracts, we identified 10 studies (5, 36–43) for inclusion (Appendix Figure 2). We identified 1 additional study by manually searching references (37). Of these 11 studies, none was a prospective cohort study comparing survival, complications, or both in patients with and without hereditary hemochromatosis defined by an elevated serum ferritin level.

Regarding the relationship between primary iron tissue deposition and hereditary hemochromatosis–related disease, an electronic search through 20 April 2004 identified 259 unique postings. After reviewing the titles and abstracts, we identified 13 original studies (7, 45–56) (Appendix Figure 3). Seven studies explored the relationship of hereditary hemochromatosis and survival, and the remainder evaluated the association of hereditary hemochromatosis with other complications.

Subquestion 3: How Diagnostically Useful Are Transferrin Saturation and Serum Ferritin Level in Identifying Primary Care Patients with Hereditary Hemochromatosis?

We examined the medical literature to determine the diagnostic efficacy of common tests used to assess iron overload (elevated transferrin saturation on 2 occasions, elevated serum ferritin level, or both) in predicting the presence or absence of hereditary hemochromatosis as previously defined. We used the PubMed Clinical Queries filters for diagnosis and the terms *he-*

hereditary hemochromatosis, hemochromatosis, transferrin saturation, and serum ferritin. We included original studies that were conducted in a primary care setting that addressed the diagnostic usefulness of transferrin saturation or serum ferritin level in predicting hereditary hemochromatosis defined by liver biopsy or response to therapeutic phlebotomy.

The electronic search identified 375 unique postings. Of these, we identified 7 for possible inclusion (21–23, 25, 27, 28, 68). We identified 2 additional studies by reviewing references (20, 29). Only 3 studies (20–22) were conducted in the primary care setting (Appendix Figure 4). No studies independently and blindly compared the screening tests for iron overload (transferrin saturation and serum ferritin) with the gold standard (liver biopsy or mobilizable iron by phlebotomy) in all screened patients.

Subquestion 4: Is Phlebotomy Efficacious in Reducing Morbid or Fatal Complications in Asymptomatic Patients with Hereditary Hemochromatosis?

On the basis of large uncontrolled case series, most hepatologists have accepted the efficacy of phlebotomy for improving survival in patients without cirrhosis (7). This acceptance has made it difficult to conduct prospective, controlled comparisons (cohort studies or randomized, controlled trials) for ethical reasons. However, we assessed the rigor of the available literature for answering this question. We searched for controlled comparisons of phlebotomy in asymptomatic patients with iron overload or in patients with liver iron deposition but without cirrhosis. We used the PubMed Clinical Queries filters for treatment and the terms *hereditary hemochromatosis, hemochromatosis, survival, and diabetes mellitus, congestive heart failure, arthritis, cirrhosis, and hepatocellular carcinoma.* We included original studies conducted in a primary care setting or in a representative sample of the general population that addressed the usefulness of therapeutic phlebotomy in patients with hereditary hemochromatosis. We looked for differences in diabetes mellitus, congestive heart failure, arthritis, cirrhosis, hepatocellular carcinoma, and survival in patients receiving or not receiving therapeutic phlebotomy.

An electronic search of MEDLINE identified 409 unique postings. We identified only 1 study for inclusion because it compared those adequately phlebotomized with those inadequately phlebotomized (46). We identified 1 additional study by

manual search (7) because of its before–after phlebotomy comparison of liver histology (Appendix Figure 5).

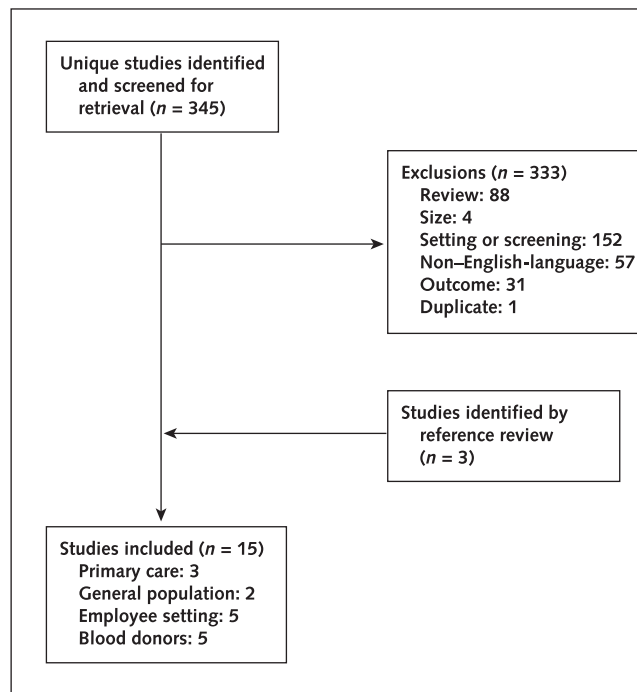
Subquestion 5: Do the Benefits Outweigh the Risks in Screening Primary Care Patients for Hereditary Hemochromatosis?

A review for evidence of the effectiveness of hereditary hemochromatosis screening in the primary care setting was contingent on identification of studies to establish the efficacy of screening within a research setting. To assess the balance of benefits and risks identified in subquestion 4, we evaluated all integrative secondary data analyses (decision analysis or cost-effectiveness analysis) that modeled the benefits and harms of a screening program in primary care. To be included, the model had to compare some form of phenotypic hereditary hemochromatosis screening with no screening.

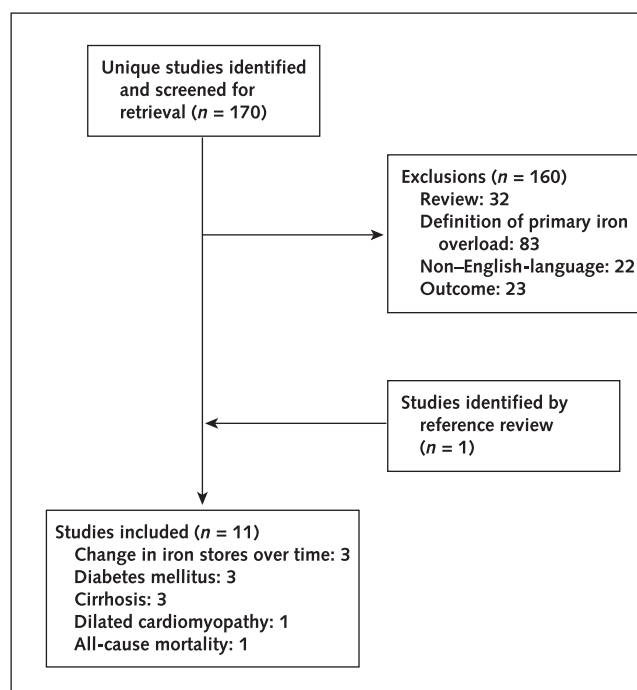
The electronic literature search for a decision analytic model of a cost-effectiveness analysis identified 4 unique postings. We included 1 (60) in our review. The 3 excluded postings were not decision-analytic comparisons. Manual search of references identified 8 additional references for possible inclusion (14, 20, 58, 59, 61–63, 66). We excluded the studies by Balan and colleagues (66) and Baer and colleagues (20) because they did not model costs or effects across 2 or more screening options. They simply provided the costs involved in screening patients in a clinic setting. We excluded 2 additional studies because they evaluated the cost-effectiveness of screening family members of heterozygotes (14, 63). No studies specifically evaluated the cost-effectiveness of screening within the primary care setting. The remaining studies addressed general population screening, and we included them for review. Two (58, 59) were previously reviewed in *Annals of Internal Medicine* (13). Cogswell and colleagues (13) identified the major determinants of screening cost-effectiveness: prevalence and disease burden; sensitivity and specificity of the screening tests; adherence to screening, diagnosis, and therapy; and costs of screening, diagnosis, and therapy. The lack of data on natural history led decision analysts to use data from hospital registries of patients affected with hemochromatosis, increasing the possibility of overestimation of morbidity and mortality.

We evaluated 2 studies (61, 62), which have been published since Cogswell and colleagues' comprehensive review (13), for new insights.

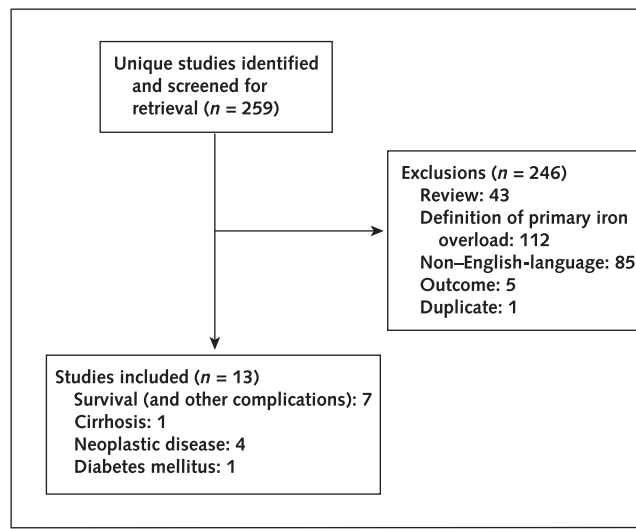
Appendix Figure 1. The selection and exclusion of articles to address subquestion 1 about the prevalence of hereditary hemochromatosis.



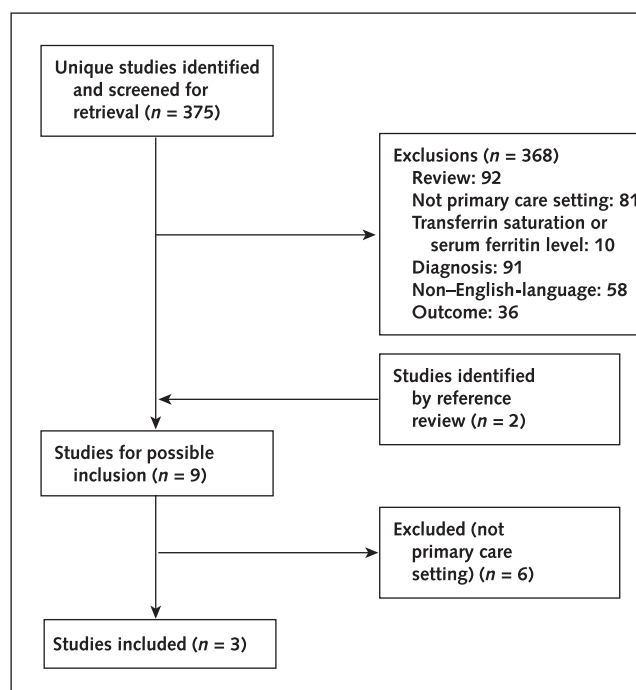
Appendix Figure 2. The selection and exclusion of articles to address subquestion 2 about the magnitude of complications with primary iron overload (biochemical measures).



Appendix Figure 3. The selection and exclusion of articles to address subquestion 2 about the magnitude of complications with primary iron overloading (iron deposition).



Appendix Figure 4. The selection and exclusion of articles to address subquestion 3 about the diagnostic usefulness of transferrin saturation and serum ferritin level.



Appendix Figure 5. The selection and exclusion of articles to address subquestion 4 about the treatment of hereditary hemochromatosis.

