Screening for Hereditary Hemochromatosis: A Systematic Review for the U.S. Preventive Services Task Force

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Background: The U.S. Preventive Services Task Force (USPSTF) has not previously considered screening for hereditary hemochromatosis for a recommendation as a clinical preventive service for primary care clinicians.

Purpose: To conduct a focused systematic review of hereditary hemochromatosis screening relating to 2 USPSTF criteria, the burden of suffering and the potential effectiveness of a preventive intervention, to determine whether evidence is sufficient for a USPSTF recommendation.

Data Sources: MEDLINE, CINAHL, and Cochrane Library databases from 1966 through February 2005. The authors supplemented literature searches with source materials from experts in the field and the bibliographies of key reviews and included studies.

Study Selection: Studies were retrieved to answer 3 key questions: 1) What is the risk for developing clinical hemochromatosis among those with a homozygous C282Y genotype? 2) Does earlier therapeutic phlebotomy of individuals with primary iron overload due to hereditary hemochromatosis reduce morbidity and mortality compared with treatment after diagnosis in routine clinical care? 3) Are there groups at increased risk for developing hereditary hemochromatosis that can be readily identified before genetic screening? The authors critically appraised studies using quality criteria specific to their design.

Data Extraction: The authors abstracted all studies into evidence tables using condition definitions and diagnostic criteria.

Data Synthesis: Data were insufficient to define a very precise estimate of penetrance. Available data suggest that up to 38% to 50% of C282Y homozygotes may develop iron overload, with up to 10% to 33% eventually developing hemochromatosis-associated morbidity. Prevalence of C282Y homozygosity is higher in family members of probands and other high-risk patient groups defined by signs, symptoms, and phenotypic screening.

Limitations: This review considered genetic screening for *HFE*-related hereditary hemochromatosis in C282Y homozygotes only. Available research is limited, is based solely on observational designs, and is plagued by poor or inconsistent reporting.

Conclusions: Research addressing genetic screening for hereditary hemochromatosis remains insufficient to confidently project the impact of, or estimate the benefit from, widespread or high-risk genetic screening for hereditary hemochromatosis.

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The U.S. Preventive Services Task Force (USPSTF) has not previously considered screening for hereditary hemochromatosis for a recommendation as a clinical preventive service for primary care clinicians. We examined key questions to assess hemochromatosis penetrance in C282Y homozygotes (key question 1), address health outcomes of therapeutic phlebotomy (key question 2), and examine the possibility of targeted genetic screening (key question 3). Key questions for this focused systematic review were limited to addressing critical evidence gaps in order for the USPSTF to recommend screening (1, 2), and were applied using strict and consistent definitions of disease, which are described in more detail below.

Background

Condition Definition

Hemochromatosis was originally thought to be a rare idiopathic disorder characterized by end-stage disease (cirrhosis, diabetes, and bronzed skin) but is now recognized as having a hereditary component due to an autosomal recessive inherited disorder of iron metabolism (3). In hemochromatosis, body iron accumulates and can lead to iron overload (4). In iron overload, excess iron is deposited in the liver, pancreas, heart, joints, and endocrine glands, resulting in tissue damage that can lead to disease conditions (such as cirrhosis, diabetes, heart failure, arthropathy, and impotence) (4–6). Iron overload can be primary (as in

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hereditary hemochromatosis) or secondary (for example, due to anemias with inefficient erythropoiesis or repeated blood transfusions) (7).

In 1996, 2 base-pair alterations, termed C282Y and H63D, of the *HFE* gene on the region of *HLA-A* on chromosome 6 were identified in hereditary hemochromatosis (8). C282Y homozygosity is now recognized as the most common genotype in hereditary hemochromatosis (9). Estimates are that 82% to 90% of cases of hereditary hemochromatosis among white persons occur in C282Y/C282Y homozygotes (10). The other 10% to 18% of cases appear to be due to environmental factors or other genotypes. While other *HFE*-related and non–*HFE*-related genetic mutations are associated with hereditary hemochromatosis in a small number of cases (4), other genotypes do not appear to be as strongly associated with hereditary hemochromatosis (3, 9).

HFE mutations are fairly common in the United States, with 1 in 10 white persons heterozygous for the *HFE* C282Y mutation (carriers) and 4.4 homozygotes per 1000 (4, 6). The frequency of C282Y homozygosity is much lower among Hispanic persons (0.27 in 1000), Asian Americans (<0.001 per 1000), Pacific Islanders (0.12 per 1000), and black persons (0.14 per 1000) (11). The availability of genotyping has permitted identifying persons who have the susceptible genotype but have little or no evidence of disease. Thus, individuals homozygous for the C282Y genotype can be characterized in 1 of 4 general stages: genetic predisposition without any other abnormality; iron overload without symptoms; iron overload with early symptoms; and iron overload with organ damage, especially cirrhosis (4). Clinically recognized hereditary hemochromatosis is twice as common in males and occurs predominantly in white populations (12). While the natural history is not well understood, the condition appears to have a long latent period, with wide individual variation in biochemical expression (13). This is because iron accumulation and disease expression are modified by environmental factors, such as blood loss from menstruation or donation, alcohol intake, diet, and comorbid disease (for example, viral hepatitis) (14, 15). If symptomatic organ involvement develops, it generally occurs in mid-life with nonspecific signs and symptoms (such as unexplained fatigue, joint pain, and abdominal pain) (14). Age of onset is delayed in females (16), perhaps because of blood loss through menstruation (3). The liver is the first target organ thought to be affected by iron accumulation (17) and is central to both diagnosis and prognosis (13).

While a clinical diagnosis is based on serum iron studies and clinical evaluation, documented iron overload relies on 1 of 2 methods: quantitative phlebotomy with calculation of the amount of iron removed, or liver biopsy with determination of quantitative hepatic iron (18). Although liver biopsy was once essential to the diagnosis, it is currently used more as a prognostic tool (19). While hepatic iron concentration greater than 283 μmol/g (reference range, 0 to 35 μmol/g) is associated with cirrhosis in C282Y homozygotes (20), many patients with much higher levels do not have cirrhosis (13). Even in the absence of systemic iron overload, iron accumulates when the liver is inflamed or cirrhosed because of other causes (such as alcoholic steatohepatitis, transfusion and chronic hemolytic disorders, or chronic viral hepatitis) (21).

Cirrhosis is a late-stage disease development and has been reported to shorten life expectancy (22–25). Cirrhosis is also a risk factor for hepatocellular carcinoma (13) and typically occurs between the ages of 40 and 60 years (6). Cirrhosis prevention would be a major goal of screening and treatment (26).

Prevalence and Burden of Disease

Estimates of the general population prevalence of hemochromatosis vary because of the long preclinical period and lack of a consistent "case" definition. The prevalence of cases of hemochromatosis defined biochemically (elevated serum iron indices) will be higher than the prevalence of cases based on documented iron overload, with or without clinical signs and symptoms. The prevalence will be lowest for cases based on diagnosed disease (cirrhosis, diabetes) (27). Experts have recommended defining iron overload as distinct from hemochromatosis (4), and this provides an objective, although not universally accepted, standard for "early disease" based on documented increases in body iron stores (27).

On the basis of clinically diagnosed hemochromatosis or hemochromatosis-compatible disease, 79 850 hemochromatosis-associated hospitalizations (2.3 per 100 000 residents) were projected in the United States over 18 years (1979 to 1997), although annual rates could not be reliably calculated (28). Of 29 million deaths from 1979 to 1992, 4858 (0.017%) were consistent with hemochromatosis as an underlying cause (12). Age-adjusted mortality rates for hemochromatosis-consistent deaths increased from 1.2 per million in 1979 to 1.8 per million in 1992. These rates were about twice as high in males as in females and in white persons as in nonwhite persons. Both of these estimates of the burden of disease suggest a disease prevalence much lower than the prevalence of associated genetic mutations, which has fueled the debate about disease penetrance. While these statistics are probably underestimates, primarily because of underdiagnosis (29), the extent of this underestimation is not clear. The prevalence of hemochromatosis-attributable morbid conditions (such as cirrhosis, diabetes, arthralgias, and fatigue or other symptoms) has been proposed as an estimate of the burden due to undiagnosed disease, particularly since diagnosis may commonly be delayed as a result of the nonspecific nature of hemochromatosis-related signs and symptoms (30). Since these signs and symptoms are also prevalent and nonspecific, however, relevant evidence must establish their prevalence due to iron overload, or their excess prevalence in association with iron overload compared with controls. In

a previous study, 297 middle-aged patients with previously undetected hereditary hemochromatosis (homozygous for C282Y) had a higher prevalence of diagnosed osteoarthritis, knee symptoms, hypothyroidism, and use of antihypertensive or thyroid replacement medications than sex- and age-specific controls (31). However, general health, mental health, and 52 other questionnaire-based and clinical examination–based measures of cardiovascular, respiratory, and liver diseases were not statistically different between case-patients and controls. In another cross-sectional comparison of 124 C282Y screening-detected adult homozygotes with 22 394 wild-type/wild-type genotypic controls, common symptoms (chronic fatigue, joint symptoms, impotence, and limited general health) and signs (diabetes) were no more frequent in C282Y homozygotes than controls (32). While the relative risk for physician-diagnosed liver problems or hepatitis was increased (relative risk, 2.1 [95% CI, 1.1 to 4.0]), the proportion of C282Y homozygotes with liver problems was modest (10%). Similarly, in the Hemochromatosis and Iron Overload Screening (HEIRS) study, C282Y homozygotes had an increased odds of self-reported liver disease (odds ratio, 3.28 [CI, 1.49 to 7.22]) compared with wild-type controls. Almost one fourth, however, were not identified by screening (11). Clearly, the prevalence of hemochromatosis-attributable morbid conditions is not a simple, reliable way to estimate the disease burden associated with hemochromatosis.

Rationale for Population Screening

Screening for hemochromatosis or iron overload is theoretically attractive and has been widely discussed over the past 10 to 15 years, with renewed interest and a focus on hereditary hemochromatosis since the discovery of the *HFE* mutations (4, 33–36). Although hereditary hemochromatosis appears to be ideal for population screening (7, 16, 37–39) and for a "new paradigm for genetics and public health" (34), inadequacies in the evidence supporting genetic screening for hereditary hemochromatosis have precluded widespread support for population-based screening (4, 9, 34, 40).

Aims of Focused Systematic Review

This review addresses 2 major uncertainties in the evidence: "How much disease is actually caused by *HFE* mutations?" and "Does therapeutic phlebotomy treatment, initiated through earlier identification of those with hereditary hemochromatosis, lead to better outcomes?" We also considered evidence for high-risk (as opposed to general population) screening.

Methods

We focused on hereditary *HFE*-associated hemochromatosis due to C282Y homozygosity in persons of northern European descent, which is the most prevalent form of hereditary hemochromatosis in the United States. Other *HFE* and non-*HFE* genetic mutations are much rarer causes of hemochromatosis (41), and data for their disease association are more sparse than those for C282Y homozygosity (9).

Key Questions

We developed 3 explicit questions with supporting definitions (Appendix, available at www.annals.org), in conjunction with USPSTF leads and Agency for Healthcare Research and Quality (AHRQ) staff.

Key question 1: What is the risk for developing clinical hemochromatosis among those with a homozygous C282Y genotype?

Key question 2: Does earlier therapeutic phlebotomy of individuals with primary iron overload due to hereditary hemochromatosis reduce morbidity and mortality compared with treatment after diagnosis in routine clinical care?

Key question 3: Are there groups at increased risk for developing hereditary hemochromatosis that can be readily identified before genetic screening?

Data Sources

We developed literature search strategies and terms for each key question (**Appendix Table 1**, available at www.annals.org) and conducted 4 separate literature searches (for key questions 1, 2, and 3 and for background) in the MEDLINE, CINAHL, and Cochrane Library databases from 1966 through February 2005. Literature searches were supplemented with source material from experts in the field and by examining the bibliographies of included studies. A single investigator reviewed abstracts, and a second reviewer independently reviewed all excluded abstracts. Interreviewer discrepancies were resolved by consensus.

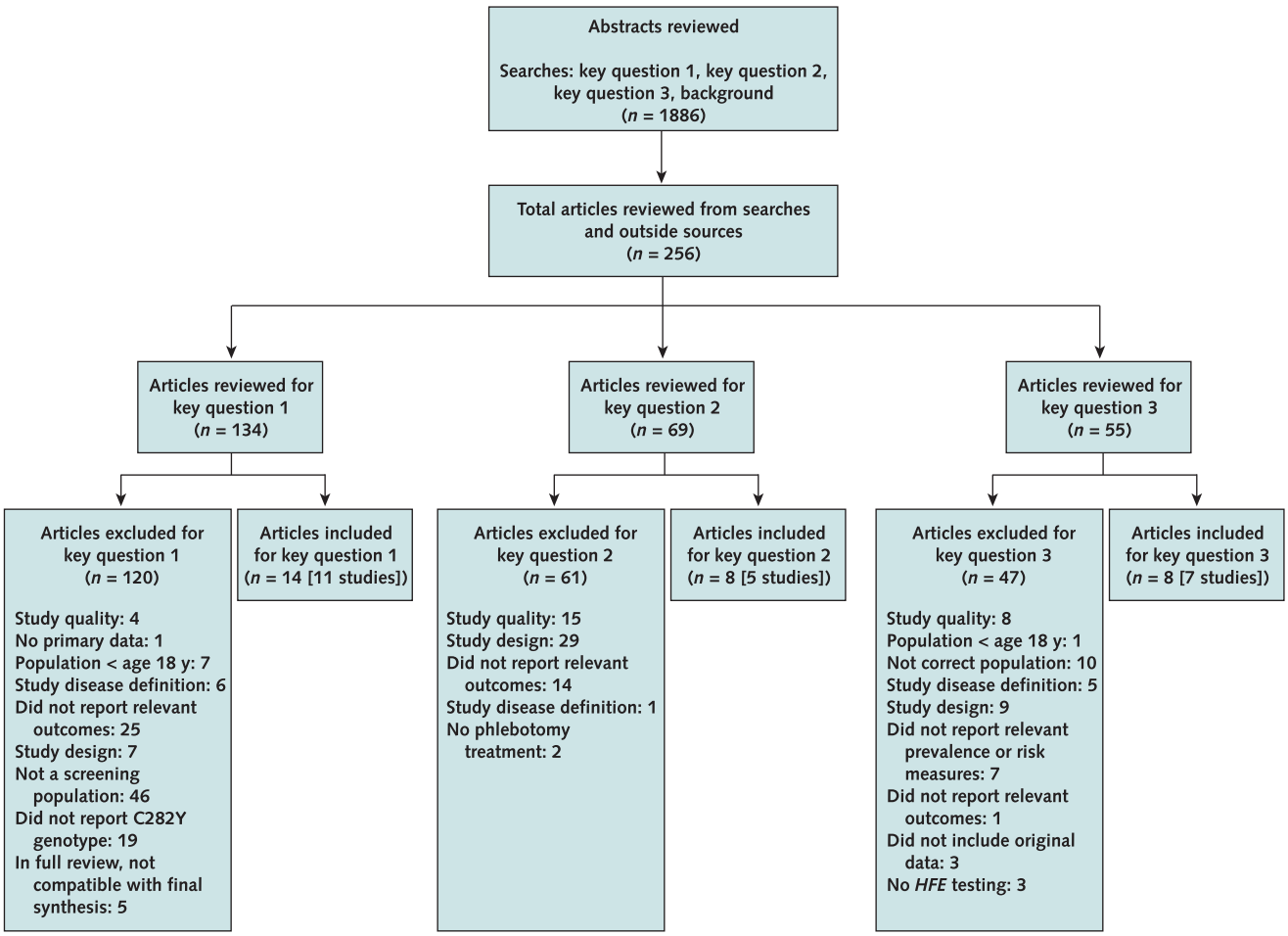
Study Selection

Using inclusion criteria developed for each key question (described in **Appendix Table 2**, available at www.annals.org), we reviewed 1886 abstracts for inclusion in all key questions (**Figure**). Literature searches were focused for each key question but were reviewed with all key questions in mind. We reviewed 134 full-text articles for key question 1, 69 articles for key question 2, and 55 articles for key question 3. Two investigators rated all included articles for quality, as well as those excluded for quality-related reasons, using the USPSTF criteria (**Appendix Table 3**, available at www.annals.org). Excluded articles are listed in **Appendix Tables 4** to **6** (available at www.annals.org).

Data Extraction and Quality Assessment

To overcome the inconsistent uses of terminology in the literature, we adopted the set of terms in the Appendix for extracting data from studies into tables in a consistent format. We also established a priori screening and diagnostic criteria for elevated iron measures and iron overload due to hereditary hemochromatosis to guide our review and to establish comparability between studies (**Table 1**; 42–45). Data were abstracted into evidence tables by a single re-

Figure. **Search results and article flow by key question.**



viewer and checked by a second reviewer (**Appendix Tables 7** to **10**, available at www.annals.org; 25, 32, 46–67).

We critically appraised studies according to USPSTF methods (67) using quality criteria specific to their design (**Appendix Table 3**). To augment criteria provided for nonrandomized studies of treatment effectiveness, we added criteria from the Cochrane Non-Randomised Studies Methods Group (68). We eliminated any case series or nonrandomized comparative treatment study that used a nonsystematic method of case accrual. We critically evaluated reported results, including the comparability of constructed comparison groups, concerning whether confounding factors (age, sex, alcohol intake, population prevalence of C282Y homozygosity, and comorbid liver disease) and secular trends in disease diagnosis and medical care were adequately considered. We eliminated studies with possible serious biases.

Data Synthesis

Studies were extremely heterogeneous and could not be easily synthesized quantitatively. To evaluate whether our review identified adequate data to create one or more outcomes tables for illustrating the expected yield from screening, we used an approach adapted from a previous report (35). We considered whether there were adequate data for genetic screening of 2 different screening populations (general population and family-based). Insufficient data were available to create a reliable outcomes table for either screening approach since very few studies reported results for all required measures (genotype, iron measures, iron overload, and disease) among screening study participants, resulting in extremely small numbers for within-study morbidity estimates. Therefore, we summarized screening data in tables, as described later.

We selected data from studies that met minimum a priori criteria for 3 variables: 1) screening positive for elevated iron measures, 2) documented iron overload, and 3) morbidity due to clinical hemochromatosis. For iron overload and morbidity, we calculated 2 proportions (selected and all). Among patients selected for further evaluation, we reported the proportion of positives among those who were

actually tested for iron overload or morbidity (maximum penetrance) and, for all, the proportion who screened positive among all those evaluated at the first screening step (minimum penetrance). We evaluated whether results were similar enough to combine across studies and, when they were, we quantitatively combined study results for each variable to generate a single point estimate for that variable. We reported a range of results for any variable for which individual study results were too different to be meaningfully combined. We did not include individual study results with 10 or fewer patients in the denominator to define a range, but we did include these results if they could be combined with other results in a single variable estimate. Study results were reported as raw numbers for denominators of 10 or fewer.

Role of the Funding Source

This research was funded by AHRQ under a contract to support the work of the USPSTF. The USPSTF members participated in the initial design and reviewed interim results and the final evidence review. Although AHRQ had no role in the study design, data collection, or synthesis, AHRQ staff reviewed interim and final evidence reports and distributed the initial evidence report for external content review by 7 outside experts, including representatives of professional societies and federal agencies. The subsequently revised systematic review on which this manuscript is based is available at www.ahrq.gov/clinic/serfiles.htm.

Table 1. **Screening and Diagnostic Criteria for Iron Overload**

Term/Test*	Men	Women
Screening-positive for elevated iron measures		
Transferrin saturation, % (42–44)	>50	>45
Serum ferritin level, μg/L (44, 45)	>300	>200
Possible iron overload		
Repeat transferrin saturation, %	>50	>45
or		
Repeat serum ferritin, μg/L	>300	>200
or		
Initial increased transferrin saturation and serum ferritin level PLUS clinical examination		
Provisional primary iron overload (44)		
Repeated transferrin saturation shows increased serum ferritin levels not due to liver disease, inflammation, or secondary causes of iron overload		
Iron overload: documented (44)		
Meets all the provisional primary iron overload criteria and shown to have increased body iron stores by ≥1 of the following:		
Hepatic iron concentration (biopsy): ≥90 μm/g, ≥5000 μg/g dry weight		
Iron removed to reach iron depletion (phlebotomy): ≥4 g iron removed		
Histology: suggestive of hemochromatosis and Hepatic iron index: ≥1.9 or Hepatic iron staining: 3+, 4+		

* Numbers in parentheses are reference citations.

DATA SYNTHESIS

Key Question 1. What Is the Risk for Developing Clinical Hemochromatosis among Those with a Homozygous C282Y Genotype?

Of 134 full-text studies examined, we excluded 120 studies for reasons specified by our inclusion and exclusion criteria (**Appendix Table 4**). We eliminated all studies that combined outcome measures for C282Y homozygotes from more than one population source (for example, from family, clinical, or healthy population screening) since disease expression potentially differs among these groups. We eliminated studies that did not report data on morbid conditions associated with clinical hemochromatosis (or at least iron overload) among participants. We had 2 other main categories for study exclusion: 1) studies that involved groups of homozygotes that did not derive from any definable population—particularly one that could be subject to screening; and 2) studies with data reported in ways that did not conform to our hemochromatosis-related definitions. One study was identified, but not yet published, at the time we prepared this manuscript (**Appendix Table 11**, available at www.annals.org). Two studies supplied data that did not meet requirements for our final data synthesis (69, 70); 3 studies on genotyping in blood donors (71–73) were not relevant to this paper but are included in our full evidence report (74).

Table 2 summarizes the findings for this key question. The best evidence is from 2 fair- to good-quality longitudinal studies reporting the risk for developing disease in initially nondiseased C282Y homozygotes (46, 47). Although neither was done in an inception cohort, these retrospective cohort studies from Australia (46) and Denmark (47) reported on disease expression (penetrance) of 33 C282Y homozygotes (22 women and 11 men) over 17 to 25 years of follow-up. Participants' average age at the end of observation was 47 to 63 years. Most, but not all, C282Y homozygotes (61% to 75%) developed some elevations in serum iron measures during follow-up. When compared with other age- and sex-matched genotypes, C282Y homozygotes tended to have higher mean transferrin saturation and serum ferritin levels, and average measures generally increased with age among all genotypes (47). However, C282Y homozygotes also showed more individual variation in serum iron measures than other genotypes, and many individuals did not show steady increases in these measures over time (46, 47). For example, neither blood loss nor donation explained the substantial decreases in serum ferritin levels over 17 years seen in 2 of 10 C282Y homozygotes (46). The Australian study (46) objectively evaluated iron overload using liver biopsy in the 6 of 10 participants who developed serum ferritin levels greater than 500 μg/L. At least moderate iron overload (see Appendix for definition) was detected in 5 patients who underwent biopsy (representing 5 of 10 total study participants). Two of the patients who underwent biopsy had

Table 2. **Genotypic Screening Yields***

Study, Year (Reference)	Prevalence of C282Y Homozygotes	Elevated Transferrin Saturation in Homozygotes	Elevated Serum Ferritin Level in Homozygotes	Patients with Iron Overload Due to Hereditary Hemochromatosis	Patients with Diabetes†	Patients with Other Diseases/Elevated LFT Results†	Fibrosis or Cirrhosis†
Longitudinal: general population (2 studies)							
Andersen et al., 2004 (47)	2.5/1000	Men: 5 of 7 (71%) Women: 9 of 16 (56%) (both tests elevated)		Selected C282YY: ND All C282YY: ND	All C282YY: 1 of 23 (4.4%)	Liver disease: 0 of 23 Hypogonadism: 0 of 23 Cardiomyopathy: 0 of 23 Arthralgia: 2 of 23 Subclinical hemochromatosis: 1 of 23	ND
Olynyk et al., 2004 (46)	4/1000	Men: 4 of 4 (100%) Women: 2 of 6 (33%) (both tests elevated)		Selected C282YY: 5 of 6 (83%) All C282YY: 5 of 10 (50%)	1 of 10	Arthralgia: 4 of 10	Selected C282YY: 3 of 6 (1 also consumed alcohol) All C282YY: 3 of 10 (30%)
Cross-sectional studies							
General population (7 studies)							
Total population: n = 67 771 (32, 51–56) Total patients with C282YY studied: n = 282	4.2/1000	Men: 75%–94% Women: 40%–94%	Men: 58%–76% Women: 54%–58%	Selected C282YY‡: 26 of 69 (38%) All C282YY‡: 30 of 127 (24%)	All C282YY: 0%–5.6%	All C282YY: LFT, ND	Cirrhosis or fibrosis§: Selected C282YY: 5 of 16 (31%) All C282YY: 5 of 72 (6.9%) Fibrosis§: Selected C282YY: 4 of 16 (25%) All C282YY: 4 of 72 (6%) Cirrhosis§: Selected C282YY: 1 of 16 (6%) All C282YY: 1 of 72 (1.4%)
Family history (2 studies)							
Barton et al., 1999 (57) Total sample: n = 150 Total patients with C282YY studied: n = 25	161/1000	Men and women: 87.5%	Men and women: 96%	All C282YY: ND	All C282YY: 16%	All C282YY: ND	Selected C282YY: ND All C282YY: 2 of 25 (8%)
Powell et al., 2006 (58) Relatives of probands; total C282YY studied: n = 401	ND	ND	ND	Men: Selected C282YY: 82 of 111 (74%) Women: Selected C282YY: 46 of 74 (62%) Men: All C282YY: 82 of 200 (41%) Women: All C282YY: 46 of 201 (23%)	Men: All C282YY: 2% Women: All C282YY: 3.5%	Men: All C282YY: 24% Women: All C282YY: 7%	Cirrhosis or fibrosis: Men: Selected C282YY: 32 of 111 (29%) Women: Selected C282YY: 5 of 74 (7%) Men: All C282YY: 32 of 200 (16%) Women: All C282YY: 5 of 201 (2%) Fibrosis: Men: Selected C282YY: 25 of 111 (23%) Women: Selected C282YY: 3 of 74 (4%) Men: All C282YY: 25 of 200 (13%) Women: All C282YY: 3 of 201 (2%) Cirrhosis: Men: Selected C282YY: 7 of 111 (6%) Women: Selected C282YY: 2 of 74 (3%) Men: All C282YY: 7 of 200 (4%) Women: All C282YY: 2 of 201 (1%)

* C282YY = C282Y/C282Y; LFT = liver function test; ND = no data reported or not acceptable.
† Selected C282YY refers to percentage positive only in those tested; all C282YY refers to percentage positive in all patients with C282YY.
‡ Data from references 32, 52–55.
§ Data from references 52–54, 56.

hepatic fibrosis, while the single patient with cirrhosis reported alcohol intake greater than 6 drinks per day. In contrast, none of the 23 Danish patients had liver disease detectable by clinical examination (47). Thus, when both studies were considered together, liver disease developed in 3 of 33 C282Y homozygotes. Similarly, 2 of 33 C282Y homozygotes developed diabetes and 6 of 33 developed arthralgias. No participant developed cardiomyopathy or hypogonadism.

These retrospective cohort studies have 2 potential limitations. The first limitation relates to whether these data accurately represent lifelong disease expression in C282Y homozygotes. Despite the long follow-up period of 17 to 25 years, 8 women were 50 years of age or younger at final follow-up. Thus, 8 of 33 (24%) of those studied may not yet have reached the age at which clinical expression would be likely. Second, selective mortality bias resulting from follow-up only for survivors could have influenced these findings to represent the experience of healthier C282Y homozygotes. In the Australian study, however, the prevalence of C282Y homozygotes (5.3 per 1000) was within the population range expected, and complete data were available on 83% of the cohort (46). In the Danish study, selective mortality bias may be more likely since 35% of the original cohort did not have genotyping and 3 of the 23 C282Y homozygotes died before they could be examined (47). We calculated the upper bound for disease penetrance as follows to determine the potential impact of

selective mortality bias on this study. If all 3 C282Y homozygotes who died were counted as developing hemochromatosis, the proportion developing clinical disease would still be about one quarter (4 of 23). If the 35% of the cohort lost to follow-up had the usual population prevalence of C282Y homozygosity (5 per 1000), then about 25 C282Y homozygotes would have been lost to follow-up. If all 25 homozygotes developed clinical disease, the estimate for disease penetrance would be 60% (29 of 48) after 25 years of follow-up.

While cross-sectional studies were more plentiful, they provided an estimate of disease expression only at the time of genotype identification. Twelve papers (32, 48–58) report cross-sectional genotypic and selected phenotypic and disease expression results from 9 screening studies (**Appendix Table 8**). C282Y homozygotes were identified at 2 health clinics (32, 48–51) through mass screening (52), through voter rolls or employment screening (53–56), or through family screening (57, 58). We combined health clinics, mass screening, voter rolls, and employment screening results to represent "general population" screening based on the similarity of findings for C282Y prevalence and phenotypic expression between settings. A total of 282 C282Y homozygotes were identified from screening 67 771 patients in these general population settings, and 426 C282Y homozygotes were identified from genotyping in an unspecified number of family members of probands. The prevalence of C282Y homozygosity was 4.2 per 1000 screened in the general population and 161 per 1000 family members screened (based on the single family screening study that reported the number of family members screened) (57). Transferrin saturation levels were elevated in 75% or more of male C282Y homozygotes identified from general population screening, and the majority (58% to 76%) had elevated serum ferritin levels. Elevations of transferrin saturation and serum ferritin levels were more variable or less common among female homozygotes from the general population than among male homozygotes. Transferrin saturation and serum ferritin elevations in family members were very common (88% to 96%).

Among C282Y homozygotes identified from general population genetic screening, 38% of those undergoing further evaluation met criteria for iron overload, 25% had liver fibrosis, and 6% had cirrhosis. Data could not be reported reliably for males and females separately. These iron overload and disease estimates could be too high if the C282Y homozygotes who were not evaluated further are less likely to be penetrant. Assuming that all the untested C282Y homozygotes were unaffected, the prevalence of iron overload, hepatic fibrosis, and cirrhosis among newly screening-identified C282Y homozygotes would be 24%, 6%, and 1.4%, respectively. These estimates, however, should be viewed with caution because they are based on very small numbers. We also cannot be sure of the likelihood of disease penetrance (same, higher, or lower) in the large proportion of untested screening-identified C282Y homozygotes.

Data from genotyping of family members of probands may indicate that a higher proportion of C282Y homozygotes' relatives have evidence of iron overload, but not necessarily of clinical disease, at the time of screening compared with homozygotes identified through population screening. Among male first-degree relatives, 74% of those further evaluated have iron overload, 23% have fibrosis, and 6% have cirrhosis. Among female first-degree relatives, 62% of those further evaluated have iron overload, 4% have fibrosis, and 3% have cirrhosis. If we assume that all those not further tested were unaffected, estimates of the prevalence of iron overload, fibrosis, and cirrhosis in male C282Y homozygotes identified through family screening are 41%, 13%, and 4%. The respective prevalences for females are 23%, 2%, and 1%. Iron overload and disease expression at the time of identification were reported only for the limited number of C282Y homozygotes undergoing further evaluation for clinical reasons. Not all studies reported these measures and, within studies, variably selected participants received disease evaluations because of differences in the participants' clinical presentation, in their willingness to be tested, and in clinical practice norms. Estimates across studies cannot be easily compared because of potential detection bias and likely between-group differences in important factors in penetrance (such as age and sex) between C282Y homozygotes, particularly those identified from general population screening compared with those identified through family screening.

Key Question 2. Does Earlier Therapeutic Phlebotomy of Individuals with Primary Iron Overload Due to Hereditary Hemochromatosis Reduce Morbidity and Mortality Compared with Treatment after Diagnosis in Routine Clinical Care?

We found no controlled studies of phlebotomy treatment in patients with hemochromatosis due to any cause, nor any studies that allowed a valid comparison of early versus delayed treatment. Four fair-quality case series of patients with hemochromatosis reported objective measures before and after, or simply after, treatment (25, 58–61) in 7 publications (22, 23, 25, 58–60, 75). One retrospective observational survey (76) reported recalls of changes in symptoms after treatment among patients with hemochromatosis identified through multiple outreach mechanisms (**Appendix Table 9**). We excluded 61 full-text articles, primarily because of study quality, small size (<20 patients), or lack of primary data or relevant outcomes (**Appendix Table 5**).

Table 3 summarizes the findings for this key question. Altogether, treatment studies of patients from referral centers, who were identified and treated over a 50-year period, report on the survival experience of 447 patients over a mean duration of 8.1 (SD, 6.8) to 14.1 (SD, 6.8) years, and the reduction in morbidity after treatment of 370 pa-

Table 3. **Summary of Treatment Trials: Key Question 2***

Study, Year (Reference)	Population, *n*	Treatment	Measure and Results
Adams et al., 1991 (25)	85 Probands and family members	500 mL of blood/wk until serum ferritin level < 30 μg/L or patient became anemic	Cumulative survival, % 5 y: 87 10 y: 81 20 y: 71 Adjusted relative risk for death Cirrhosis: 5.54 Arthritis: 0.24
Niederau et al., 1996 (60)	251 Diagnosed through routine clinical practice	500 mL of blood/1–2 wk until serum ferritin levels were normal	Cumulative survival, %† 5 y: 93 10 y: 77 20 y: 55 30 y: 20

Changes in fibrosis stage after iron depletion (*n* = 185)

Stage	I, *n*	W, *n*	U, *n*
0	0	1	20
1	10	1	21
2	20	0	19
3	12	0	81
Total	42 (23%)	2 (1%)	141 (76%)

Sign/Symptom	AD, %	I, %	U, %	W, %
Weakness/lethargy	80	55	40	6
Abdominal pain	56	68	29	1
Arthralgia	45	30	50	20
Elevated AST or ALT level	81	73	25	2
Pigmentation	68	68	32	0
Loss of potency	40	19	69	12
Electrocardiographic changes	35	34	61	5
Diabetes mellitus	44	41	53	6
Impaired glucose tolerance	15	37	56	7

Bomford and Williams, 1976 (59)	Treated: 85 Controls: 26 Diagnosed through routine clinical practice	600 mL of blood/wk until hemoglobin value ≤ 100 g/L and serum iron level < 10 μmol/L	Diabetes, *n/n (%)* Improved: 16/56 (29) Worsened: 7/56 (13) New cases: 3 Liver histologic features, *n/n (%)* Improved: 5/75 (7) No definite change: 68/75 (91) Worsened: 2/75 (3)
McDonnell et al., 1999 (55)‡	2851 Population-based mailing to persons known to have hemochromatosis	Varied	Some or all of symptoms improved with therapy: 86% New symptoms developed despite treatment: 33%

Sign or Symptom	All Patients, *n (%)*	I, *n (%)*§	W, *n (%)*‖
Extreme fatigue	1296 (45.5)	705 (54.4)	223 (17.2)
Joint pain	1241 (43.5)	115 (9.2)	422 (34.0)
Impotence/loss of libido	735 (25.8)	93 (12.7)	204 (27.8)
Skin bronzing	733 (25.7)	431 (58.8)	30 (4.1)
Heart fluttering	679 (23.8)	42 (6.2)	69 (10.1)
Depression	592 (20.8)	242 (40.8)	61 (10.3)
Abdominal pain	578 (20.3)	129 (22.3)	69 (11.9)

Powell et al., 2006 (58)	25 Selected subset of cases diagnosed through family screening or work-up of elevated iron measures	Unspecified	Change in fibrosis stage after iron depletion, *n/n (%)* Improved: 19/20 (95) Unchanged (cirrhosis at baseline): 1/20 (5) Not reported because of high alcohol intake: 5/25 (20)

* AD = at diagnosis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; I = improved; U = unchanged; W = worsened.
† Significantly reduced compared with expected survival in matched population.
‡ Compared with National Health and Nutrition Examination Surveys II and III, similar proportion of patients reported arthritis, liver or gallbladder disease, and extreme fatigue as general population.
§ Improved with treatment.
‖ Worsened despite treatment.

tients with hemochromatosis (25, 58–60). Only 105 of these patients had genetically confirmed hereditary hemochromatosis (25, 58), and, of these, source of detection (clinical detection or family screening) was available for 85 patients (56% were probands and 44% were family members) (25). Fewer patients with confirmed hereditary hemochromatosis had cirrhosis at diagnosis (3.4% [58] to 32% [25]), compared with reports from patients whose condition was not genetically confirmed (57% [60] to 79% [59]); these findings are consistent with strong secular trends in disease severity at diagnosis (60). Secular trends in survival were also apparent, since survival improved over 10 years of follow-up in patients in whom hemochromatosis was diagnosed in 1982 to 1991, compared with 2 groups who received the diagnosis earlier ($P \leq 0.05$, log-rank test) (60). For patients whose hemochromatosis was diagnosed during this later time (1982 to 1991), cumulative survival was not significantly reduced from rates expected for an age- and sex-matched population (60). Similarly, patients with genetically confirmed hemochromatosis who did not have cirrhosis at diagnosis experienced the same survival as population controls (25).

Among treated patients with hereditary hemochromatosis, cirrhosis at diagnosis appeared to confer a worse prognosis (adjusted relative risk for death, 5.54 [CI, 1.76 to 17.47]) (25). However, comparisons of survival differences between cirrhotic and noncirrhotic patients, between other patient subgroups (for example, diabetic vs. nondiabetic patients [60] or between all patients and historical controls [59]) are not completely reliable because of potential confounding by uncontrolled and unmeasured factors, such as era of diagnosis, age at diagnosis, sex, excessive alcohol use, concomitant hepatitis, and dietary factors.

In the best available evidence on the effects of phlebotomy treatment, pretreatment and post-treatment liver biopsies in 260 patients who received a diagnosis through routine clinical practice suggest some reversibility of hepatic disease, with 7% to 23% showing improvement and 1% to 3% showing worsening (59, 60). Improvement in histologic characteristics was more common (32.6%) in patients with less severe, precirrhotic liver disease than in patients with cirrhosis (14.8% improved) (60). In a highly selected subgroup of family (and health check) screening-detected patients ($n = 25$) who underwent a second biopsy after treatment for persistently elevated liver enzyme levels or uncertainty about cirrhosis on first biopsy, 19 of 20 showed improvement in hepatic fibrosis scores after treatment; the only case with baseline cirrhosis was unchanged (58). These findings are not clearly generalizable because of the selected nature of the patient group and because biopsy results in 5 cases with high alcohol intake were not reported.

Several studies suggest that some, but not all, other disease process and symptoms will respond to phlebotomy treatment. In 183 primarily male symptomatic patients (57% of whom had cirrhosis) who received a diagnosis before 1991, 41% of those with type 1 diabetes mellitus reduced their daily dosage; 73% with elevated levels of liver enzymes (alanine aminotransferase or aspartate aminotransferase) showed improvement; and symptoms such as weakness, lethargy, or abdominal pain improved in more than half (60). Improvements in arthralgias (30%) and potency (19%) were less prominent. A total of 2851 primarily male patients with hemochromatosis, most of whom received a diagnosis after 1990 through family screening or an abnormal laboratory test finding, were asked to recall their experience before and after treatment. They reported comparable improvements in extreme fatigue (50%), abdominal pain (22%), impotence (13%), and joint pain (9%). Many patients also recalled improvement in depression (41%), but many (33%) also recalled onset of new symptoms after treatment (76). This study is weakened by its reliance on recall and the absence of controls to compare nonspecific symptom prevalence and changes over time.

Key Question 3. Are There Groups at Increased Risk for Developing Hereditary Hemochromatosis That Can Be Readily Identified before Genetic Screening?

We examined 55 full-text articles and excluded 47 studies from this question for various reasons (**Appendix Table 6**), such as not reporting relevant measures or results, addressing the wrong population, not using C282Y genotype to define the family risk group, using an ineligible study design, or having poor quality. One fair- to good-quality cross-sectional study of family members of genotyped probands (57) and 6 fair- to good-quality cross-sectional studies (in 7 publications) (51, 61–66) of patients with signs or symptoms consistent with iron overload or hemochromatosis met our inclusion criteria.

Table 4 summarizes the findings for this key question. Potential high-risk groups were examined for a higher prevalence of C282Y homozygosity, including 150 family members of probands and 42 636 patients with fatigue or increased liver enzyme levels from primary care or hepatology, endocrinology, and rheumatology specialty settings. Family screening identified the highest prevalence of undetected C282Y homozygotes (23% overall), particularly among siblings of probands (33% homozygosity). Among symptomatic patients selected from primary care, rheumatology, endocrinology, or referral medicine clinics, 0% to 5.8% were C282Y homozygotes, compared with 0.2% of a random sample of persons attending a health appraisal clinic (27). Overall, the prevalence of C282Y homozygosity did not differ between patients in the health appraisal clinic and primary care patients with an index sign or symptom. Compared with controls, C282Y homozygosity was significantly more prevalent only in hospitalized diabetic patients from an endocrinology clinic (5.8%) and in patients from a referral medicine clinic with chronic fatigue and arthralgias (5.7%). Three other studies confirm or extend these results. Males, but not females, with chronic

Table 4. **Prevalence of C282Y Homozygosity in High-Risk Groups***

Study, Year (Reference)	Risk Group Definition	Population	C282Y/C282Y, *n/n* (%)
Barton et al., 1999 (57)	Relatives of persons with iron overload	Offspring of proband	5/36 (14)
		Parents of proband	3/16 (19)
		Sibling of proband	14/42 (33)
Poullis et al., 2003 (63)	Outpatients referred to a liver clinic for investigation of liver disease	Liver clinic	12/667 (1.8)
		Transferrin saturation > 0.45	11/156 (7.1)
Cadet et al., 2003 (61)	Patients presenting with conditions possibly related to hemochromatosis	Rheumatology clinic	1/221 (0.45)
		Diabetes mellitus	7/121 (5.8)
		Transferrin saturation > 0.40	7/106 (6.6)
		Specialty setting: fatigue/arthritis	13/227 (5.7)
		Serum ferritin level > 300 μg/L	13/75 (17.3)
		Health appraisal: healthy volunteers	2/991 (0.2)
		Primary care	0/60 (0)
Swinkels et al., 2002 (66)	Self-referred patients fulfilling criteria for chronic fatigue syndrome (n = 88)	Patients with chronic fatigue syndrome and increased transferrin saturation and serum ferritin levels	0/8 (0)
Deugnier et al., 2002 (51)	Patients attending health appraisal center who noted risk factor on questionnaire	Men	
		Chronic fatigue	7/828 (0.85)
		No chronic fatigue	3/2180 (0.14)
		Women	
		Chronic fatigue	12/2253 (0.53)
		No chronic fatigue	28/3361 (0.83)
		Men	
		ALT level increased	1/176 (0.57)
		ALT level not increased	9/3181 (0.28)
		Women	
		ALT level increased	3/322 (0.62)
		ALT level not increased	42/5694 (0.74)
Waalen et al., 2002 (62)	Noted history of heart attack, angina pectoris, or ICD-9 code 410 or 412 in medical record	Men	
		CHD	3/1798 (0.17)
		No CHD	65/8540 (0.76)
		Women	
		CHD	3/1074 (0.28)
		No CHD	65/9117 (0.71)
Willis et al., 2002 (65)	Patients with inflammatory arthritis	Patients with arthritis	5/1000 (0.5)
		Controls	5/1000 (0.5)

* ALT = alanine aminotransferase; CHD = coronary heart disease; ICD-9 = International Classification of Diseases, Ninth Revision.

fatigue symptoms visiting a health appraisal clinic had a slightly higher (0.85%) prevalence of C282Y homozygosity than patients without symptoms (0.14%) (51). The prevalence of C282Y homozygosity in patients from a rheumatology clinic was similar to that in the general population (65). In patients with a history of coronary heart disease, prevalence of C282Y homozygosity was the same as, or lower than, that of patients without symptoms (0.17% to 0.28%) (62). Findings may not be conclusive in comparisons based on fewer than 300 patients, given the population prevalence of C282Y homozygotes (3 to 5 per 1000 white persons).

Some studies restricted genotyping to symptomatic patients who also had some laboratory abnormality. The prevalence of C282Y homozygosity was somewhat increased in a range of patients with hemochromatosis-compatible signs and symptoms and elevated iron measures (**Table 4**). Among 667 patients from a liver clinic who had elevated iron measures, 7.1% were homozygous for C282Y (63). For hospitalized patients with diabetes and patients with chronic fatigue or arthralgias who were referred to specialists, C282Y homozygosity was higher in patients with transferrin saturation greater than 0.40 or serum ferritin level greater than 300 μg/L than in patients with disease but without elevated iron measures (6.6% to 17.3% compared with 5.7% to 5.8%) (61). The sensitivity of transferrin saturation greater than 0.40 for detecting C282Y homozygosity in diabetic patients hospitalized for disease-related complications was 100%, but the specificity was 13%. In diabetic patients, the sensitivity of a serum ferritin level greater than 300 μg/L was 86% and the specificity was 56%. For patients referred for arthralgias and unexplained fatigue, transferrin saturation greater than 0.40 and a serum ferritin level greater than 300 μg/L were about equally sensitive and specific for C282Y homozygosity (100% sensitive and 65% to 67% specific). In patients from a health appraisal clinic who had elevated liver enzyme levels, the prevalence of C282Y homozygosity appeared the same (in women), or slightly higher (0.57% vs. 0.28%, in men), compared with those with normal enzyme levels (51).

DISCUSSION

We have data on the risk for developing signs or symptoms of iron overload and hemochromatosis in 33 C282Y

homozygote adults monitored over 17 to 25 years and on the burden of disease at the time of identification for an additional 228 newly identified C282Y homozygote adults from the general population. Taken together, these data suggest that up to 38% to 50% of C282Y homozygotes develop iron overload according to our criteria and up to 10% to 33% develop definite disease (fibrosis, cirrhosis, or diabetes). Much lower estimates are also compatible with available data. Findings from a large case series on the disease expression of 271 patients with hereditary hemochromatosis identified through genetic testing of those with elevated serum iron levels detected at health appraisal screening complement our review (58). Although these patients' disease expression would represent only C282Y homozygotes already exhibiting iron accumulation by definition, rates of cirrhosis (6.3%), fibrosis (10.7%), diabetes (3.6%), or any combination of these (20.6%) were similar to or marginally higher than limited results from general population screening found in our review. Available data remain too limited to clearly establish estimates of disease penetrance, since so few people have been studied in depth (only 10 C282Y homozygotes were evaluated per our criteria for iron overload or hemochromatosis in longitudinal studies), and in those studied over time, disease could still develop with longer follow-up. Indeed, 8 of 33 of those followed longitudinally were women age 50 years or younger at last follow-up, in whom disease may not have yet developed. Also, while a higher proportion clearly develop iron overload, its clinical significance is less clear than that of clinical hemochromatosis. Finally, data reported here (and elsewhere) clearly articulate that a subgroup of untreated homozygotes—perhaps even 40% (58)—do not exhibit any or progressive iron accumulation over years of follow-up, thus complicating any message that would be given to asymptomatic screening-detected individuals.

Family members of individuals with hereditary hemochromatosis are noted to be at higher risk for being homozygous, and family screening has been established as a standard of care based on HLA-typing studies of family members of probands (77, 78). We found 1 U.S. study and 1 Australian study using *HFE* genotyping to determine risk in probands and family members that support this practice. A high proportion of tested biological relatives (23%) were also C282Y homozygotes. Similarly, compared with the general population, a higher proportion (49% to 86%) of C282Y homozygotes identified from family screening met iron overload criteria, although the proportion with fibrosis and cirrhosis did not clearly differ. Direct comparisons in disease penetrance between these different types of screening-detected C282Y homozygotes have very limited value, however, because these groups may differ with regard to who receives more in-depth clinical work-up (selection bias), as well as other ways important to disease expression. For example, a recently published study reporting on C282Y homozygous persons identified over many years through family screening and through phenotypic followed by genotypic screening found significant differences in baseline characteristics between the 2 groups that could affect disease expression (58). In addition, even if it is considered the standard of care, approaches to family screening also need to consider other associated ethical, legal, social, and psychological issues (78).

Studies examining survival are limited to 4 case series reporting on a total of 447 patients who received a diagnosis between 1937 and 1989. Disease severity at diagnosis and survival showed pronounced secular trends. Patients with a more recent diagnosis are less severely affected, and with treatment they have 10-year survival rates similar to those of age- and sex-matched controls. These trends may be due to earlier diagnosis from increased clinical suspicion or enhanced family screening due to recognition of hemochromatosis as a hereditary disease leading to earlier diagnosis, or to increases in adequate treatment after diagnosis.

Liver biopsies before and after treatment suggest arresting disease progression in most individuals and a possible reduction in the severity of hepatic fibrosis, particularly in less severely affected patients. Available data are consistent with improvements in some, but not all, hemochromatosis-related morbid conditions after treatment. None of these data come from controlled trials, however, and studies do not generally ensure minimally valid measures of treatment response. No studies reported harms, limiting the ability to determine net risks and benefits of treatment. Given these caveats, treatment may result in reduced insulin doses in patients with type 1 diabetes and decreases in elevated liver enzyme levels. Symptoms such as extreme fatigue, abdominal pain, and lethargy improve in most patients, while arthralgia and impotence do not.

Some have suggested a targeted approach to screening by identifying persons with signs or symptoms consistent with undiagnosed, early-stage hemochromatosis. Primary care patients selected for symptoms or signs consistent with hemochromatosis did not have a higher prevalence of C282Y homozygosity than healthy controls, and neither did selected symptomatic or diseased patients from rheumatology or other specialty clinics. A slightly higher proportion of C282Y homozygotes could be identified by conducting genotyping only in patients from a liver clinic prescreened to have transferrin saturation greater than 0.45 (7.7% C282Y/C282Y) or by targeting diabetic patients hospitalized for poor control or complications (5.5%) or patients referred to specialists for chronic fatigue and arthralgias (5.7%). While biochemical screening with transferrin saturation and serum ferritin further enriched this patient pool, calculated specificity remained low (56% to 67%).

Overall Evidence

The quantity of evidence that met quality and relevance criteria for the focused key questions posed by this review was small, despite a very large published literature (**Table 5**). A great deal was published before the availability

Table 5. **Summary of Overall Evidence**

Key Question	Studies, *n*	Study Designs (Reference)	Quality	Conclusions
1. Penetrance of hemochromatosis	11	1 retrospective cohort study (46)	Good: Genotyping of surviving Brusselton, Australia, cohort; potential selective mortality bias appears minimal. Small numbers.	17 y of clinical data for 10 screening-detected general population C282Y homozygotes illustrates variable disease expression and incomplete penetrance. Incomplete follow-up into older age where disease penetrance increases.
		1 retrospective and prospective cohort study (47)	Fair: Genotyping of representative Danish cohort during third examination. Results are likely to be compromised by selective mortality bias due to 35% loss of follow-up. Even accounting for potential bias, disease penetrance about 60%.	Additional 23 screening-detected C282Y homozygotes from the general population also illustrates variable disease penetrance and variable patterns of iron accumulation. No liver biopsies to confirm iron overload or disease.
		9 cross-sectional studies (32, 51–58)	Fair to good: Studies compromised by frequent inclusion of already-identified C282Y homozygotes (not clearly screening-detected), by different standards for disease, and by potential selection bias due to non–protocol-based selection for further clinical work-up.	Estimates of disease in newly identified C282Y homozygotes at screening are too limited to provide confident estimates of penetrance.
2. Efficacy of phlebotomy treatment	5	4 case series (25, 58–60)	Fair to poor: Studies compromised by selective samples, reporting on cases not clearly comparable to current diagnosis and treatment, incomplete follow-up on all cases, and failure to account for possible confounders in analyses.	Total number of reported cases is quite small and represents disease experience over 50 y. There are no data to determine the benefit of earlier treatment among screening-detected compared with contemporarily diagnosed clinical cases.
		1 retrospective survey (55)	Fair: Possible recall bias in determining response to treatment.	Treatment is recalled to relieve some but not all symptoms in a survey of patients with hereditary hemochromatosis.
3. High-risk groups	7	7 cross-sectional studies (51, 57, 61–63, 65, 66)	Fair to good: Studies examined prevalence of C282Y homozygotes in various selective populations for possible targeted screening.	Patients selected on basis of certain signs and symptoms, in combination with phenotypic testing, may be at increased risk; data are still fairly limited.

of *HFE* genotyping for hereditary hemochromatosis. After reviewing 1886 abstracts and 256 full-text articles, we located only 23 fair- to good-quality studies that were relevant to some aspect of our 3 key questions on disease burden, benefits of early treatment, and high-risk groups. Some articles cited to support screening and treatment benefits in this field did not meet minimal quality or diagnostic criteria for our review, as was true of often-cited data within the studies we could include. All the reviewed evidence, including treatment studies, was observational, much of it representing the experience of a small number of relatively selected individuals, and much of it without data to allow comparisons with an unaffected or an untreated population. The published research was often difficult to interpret consistently and accurately given incompleteness and extreme variability in reporting standards. While more recent reports are of higher quality with clearer case definitions, authors still fail to acknowledge the impact that selection bias probably has on their estimates of disease expression in C282Y homozygotes; thus, the applicability of their findings to the evaluation of general population screening is limited (58).

In reviewing this field, others have included a larger range of study designs, such as modeling the expected frequency of genotyping in older populations, autopsy studies, and other circumstantial approaches. Our focused key questions did not allow incorporation of this type of evidence into our review, but it is unlikely that their inclusion would be of great use to the USPSTF given its evidence hierarchy and requirement of at least fair-quality evidence for making its recommendations (67).

Limitations

The articles we included required substantial interpretation for data abstraction and synthesis. For individual articles, we typically reviewed all tables for possibly relevant data and checked text calculations. We made every effort to report data only on adult populations relevant to screening, which required careful reading and data dissection in studies that combined cases from many sources. We excluded studies with serious discrepancies or those in which outcomes could not be related back to a sample or population source we were addressing. Many articles required further hand calculations to extract data in the most comparable

form in order to allow cross-study comparisons, and inconsistencies between tables and text in many articles complicated this process. The number of calculations and interpretation from descriptive data raise a concern about data errors. Overall, the difficulties in understanding and interpreting this literature posed challenges to meeting our usual standards of comprehensiveness and consistency.

We primarily focused on hereditary hemochromatosis as the condition of interest for this screening review and, within that, on the most common associated *HFE* genotype in the United States (C282Y homozygosity), which accounts for 85% to 90% of cases in white persons. We did not examine other hereditary causes or the impact of *HFE* heterozygosity that may account for 3% to 5% of patients with hereditary hemochromatosis. While we did not review evidence on phenotypic screening in primary care, others have recently done so (79), and the evidence has been found insufficient for phenotypic screening for hereditary hemochromatosis in the general population (80).

Conclusions

On the basis of this focused evidence review, research regarding screening for hereditary hemochromatosis remains very limited. Despite the availability of new studies in response to calls for improved research (18, 40, 81), not enough is known to allow a confident projection of the benefit from widespread genotypic screening for hereditary hemochromatosis. Data are beginning to be reported for targeted high-risk population screening approaches (for example, high-risk identification followed by phenotypic screening followed by genotypic screening), which may prove to be useful.

Recent studies suggest that disease expression or penetrance is certainly less than 100% in C282Y homozygotes identified through some method of screening. How much less than 100%, and for whom, remains uncertain. In the next year or two, the HEIRS follow-up should provide information on short-term disease expression based on clinical examinations of C282Y homozygotes; those with elevated iron measures at the time of screening, regardless of genotype; and a sample of controls. However, only self-reported disease expression data will be available on all 99 000 (genotyped and phenotyped) primary care patients, and follow-up beyond 1 to 2 years is not planned. If funding is provided, this study could be a rich resource of prospective information on disease development, as well as observational data on treatment response in contemporarily diagnosed patients with clear disease definition. Without other data, such as might come from the HEIRS study, the literature on treatment remains quite small, consisting of dated case series in fewer than 500 patients (few of whom have hereditary hemochromatosis documented by genotype). Controlled treatment trials will probably never be undertaken for ethical reasons, so higher-quality observational treatment data would be very useful.

The literature on genotyping family members of C282Y/C282Y probands is also of limited quantity because of the relatively recent availability of *HFE* testing (1996), but there is a large body of HLA-based literature on which family screening of probands has been established. Research needs in this area remain high (79).

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Appendix: Definitions

Asymptomatic: With no or only general and vague symptoms, such as arthralgias, emotional distress, fatigue, abdominal pain, and nonspecific signs, such as elevated liver function test results.

Biochemical screening: Measurement of transferrin saturation or serum ferritin to screen for primary iron overload.

Clinical hemochromatosis: Diagnosed liver disease (fibrosis, cirrhosis, liver failure, hepatocellular carcinoma), cardiomyopathy, diabetes mellitus, or arthropathy in the presence of primary iron overload.

Elevated iron measures: Increased levels of body iron as reflected by elevations in serum transferrin saturation or serum ferritin levels.

Genotypic screening: Detecting persons with, or at risk for developing, iron overload or clinical hemochromatosis through genotyping the *HFE* gene to detect C282Y homozygosity.

Groups at increased risk for developing clinical hemochromatosis: Includes asymptomatic individuals who can be identified by virtue of an associated factor or sign and who might be the focus of a targeted genetic screening program. Factors or signs could include age, sex, ethnicity, family history of iron overload or clinical hemochromatosis, and increased liver function test results. Does not include those with existing disease (diabetes mellitus, cirrhosis, cardiomyopathy) in whom the effort is to detect hemochromatosis in order to treat the disease, as this is tertiary prevention.

Hemochromatosis: Term used variously in the literature, but here to mean manifest disease determined to be due to excess body iron, but not clearly fitting more precise etiologic definitions.

Hereditary hemochromatosis: Iron overload or clinical hemochromatosis due to C282Y homozygosity.

Iron overload: Excess deposition of iron in liver diagnosed by liver biopsy or increased total body mobilizable iron diagnosed by quantitative phlebotomy. Criterion for diagnosis is liver biopsy specimen with hepatic iron index of 1.9, with or without fibrosis. In quantitative phlebotomy, iron overload represents the removal of more than 4 g of mobilizable iron to reach biochemical indicators of iron depletion. This corresponds to approximately greater than 90 μmol/g of hepatic iron or at least "moderate" iron overload (on scale of normal, mild iron overload, moderate iron overload, substantial iron overload, and severe iron overload). "Iron overload" not meeting this standard may be considered possible or provisional primary iron overload.

Morbidity: Organ damage that results in physical disability over and above that not seen in the absence of iron overload.

Phenotypic screening: Detecting persons with or at risk for developing clinical hemochromatosis through biochemical screening by using serum ferritin or transferrin saturation.

Primary iron overload: Iron overload due to an inherent, inherited defect in iron regulation.

Screening population: Group of populations of individuals who are identified and tested in a manner that is not related to their symptoms—that is, they are not *identified* through disease signs or symptoms. A screening population can be identified by their relationship to a proband, as long as their symptoms did not bring them to the attention of the researchers.

Targeted screening: Screening those identified as high risk for developing hemochromatosis (as opposed to general population screening).

Therapeutic phlebotomy: The process of repeatedly drawing blood until iron measures are within normal limits. Typical treatment schedule is 1 unit (500 mL) of blood biweekly until serum ferritin level is less than 20 μg/L. Maintenance therapy of 3 to 4 units/y is common.

Unselected hemochromatosis: Primary hemochromatosis not clearly due to C282Y homozygosity but with secondary causes eliminated. A term created to describe a category of patients with genetic disease not clearly due to C282Y.

Wild-type: In *HFE* genotyping, typically refers to individuals who do not have C282Y and/or H63D alleles, the alleles most commonly tested.

Appendix Table 1. Search Strategies*

Key Question 1

1	HEMOCHROMATOSIS/
2	hemochromatosis.ti,ab.
3	haemochromatosis.ti,ab.
4	Iron Overload/
5	iron overload.ti,ab.
6	c282y.ti,ab.
7	1 or 2 or 3 or 4 or 5 or 6
8	cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/
9	follow-up stud$.ti,ab.
10	cohort stud$.ti,ab.
11	longitudinal$.ti,ab.
12	prospective$.ti,ab.
13	INCIDENCE/
14	incidence.ti,ab.
15	predict$.ti,ab,hw.
16	natural history.ti,ab.
17	penetrance/
18	penetran$.ti,ab.
19	clinical expression$.ti,ab.
20	clinical presentation$.ti,ab.
21	clinical consequence$.ti,ab.
22	clinical feature$.ti,ab.
23	clinical manifestation$.ti,ab.
24	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25	7 and 24
26	limit 25 to (humans and english language)
27	limit 26 to "all child (0 to 18 years)"
28	limit 27 to "all adult (19 plus years)"
29	27 not 28
30	26 not 29
31	(editorial or letter or news).pt.
32	30 not 31

Key Question 2

1	HEMOCHROMATOSIS/
2	hemochromatosis.ti,ab.)
3	haemochromatosis.ti,ab.
4	Iron Overload/
5	iron overload.ti,ab.
6	1 or 2 or 3 or 4 or 5
7	BLOODLETTING/
8	blood lett$.ti,ab.)
9	PHLEBOTOMY/
10	phlebotom$.ti,ab.
11	venesect$.ti,ab.
12	7 or 8 or 9 or 10 or 11
13	6 and 12
14	Hemochromatosis/th [Therapy]
15	Iron Overload/th [Therapy]
16	13 or 14 or 15
17	limit 16 to (humans and english language)
18	limit 17 to "all child (0 to 18 years)"
19	limit 18 to "all adult (19 plus years)"
20	18 not 19
21	17 not 20
22	(editorial or letter or news).pt.
23	21 not 22

Key Question 3

1	HEMOCHROMATOSIS/
2	hemochromatosis.ti,ab.
3	haemochromatosis.ti,ab.
4	1 or 2 or 3
5	family/ or nuclear family/ or parents/ or fathers/ or mothers/ or siblings/
6	(family or families).ti,ab.
7	(relative or relatives).ti,ab.
8	sibling$.ti,ab.

Continued

Appendix Table 1—Continued

9	(mother$ or father$).ti,ab.
10	parent$.ti,ab.
11	5 or 6 or 7 or 8 or 9 or 10
12	screen$.ti,ab,hw.
13	diagnos$.ti,ab,hw.
14	di.fs.
15	12 or 13 or 14
16	4 and 11 and 15
17	target$.ti,ab.
18	4 and 15 and 17
19	Risk Factors/
20	risk factor$.ti,ab.
21	increased risk$.ti,ab.
22	high risk.ti,ab.
23	prognostic factor$.ti,ab.
24	19 or 20 or 21 or 22 or 23
25	4 and 24
26	cascad$.ti,ab.
27	4 and 26
28	Liver Function Tests/
29	liver function.ti,ab.
30	(abnormal$ adj3 liver).ti,ab.
31	(increased adj3 liver).ti,ab.
32	(elevate$ adj3 liver).ti,ab.
33	28 or 29 or 30 or 31 or 32
34	4 and 33
35	16 or 18 or 25 or 27 or 34
36	limit 35 to english language
37	limit 36 to humans
38	limit 37 to "all child (0 to 18 years)"
39	limit 38 to "all adult (19 plus years)"
40	38 not 39
41	37 not 40
42	(editorial or letter or news).pt.
43	41 not 42

Background

1	hemochromatosis)
2	hemochromatosis.ti,ab.
3	haemochromatosis.ti,ab.
4	1 or 2 or 3
5	PREVALENCE/
6	prevalen$.ti,ab.
7	5 or 6
8	4 and 7
9	HEMOCHROMATOSIS/ep [Epidemiology]
10	mo.fs.
11	"Cause of Death"/
12	Survival Rate/
13	Life Expectancy/
14	mortality.ti,ab.
15	10 or 11 or 12 or 13 or 14
16	4 and 15
17	8 or 9 or 16
18	limit 17 to english language
19	limit 18 to humans
20	limit 19 to "all child (0 to 18 years)"
21	limit 20 to "all adult (19 plus years)"
22	20 not 21
23	19 not 22
24	(letter or news or editorial).pt.
25	23 not 24

* Databases: MEDLINE, DARE (Database of Abstracts of Reviews of Effects), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials. Dates searched: 1966 to February 2005.

Appendix Table 2. Inclusion and Exclusion Criteria for Key Questions*

Key Question 1

Exclusion criteria

1. Nonhuman study
2. Non–English-language
3. Study quality: Does not meet USPSTF criteria for quality
4. Age <18 y unless adult data are broken out separately
5. Study disease definition does not meet our definition of asymptomatic primary iron overload or clinical disease (see 2 below)
6. Design: Case series, editorial, letter, case–control study, review
7. Does not report relevant prevalence or risk factors
8. Not a screening population
9. Does not include C282Y genotyping in screening sequence
10. Mediterranean populations

Inclusion criteria

1. Population: Adults ≥ age 18 y, population applicable to United States (United States, Europe, Australia, New Zealand, Canada), screening population with elevated iron measures, asymptomatic iron overload, or *HFE* C282Y homozygosity
2. Disease: Meets our disease definition (liver fibrosis, cirrhosis, hepatic failure, hepatocellular carcinoma, diabetes mellitus, cardiomyopathy, or arthropathy attributable to iron overload)
3. Design: Cohort or cross-sectional study
4. Measures: Risk or prevalence of asymptomatic iron overload

Key Question 2

Exclusion criteria

1. Nonhuman study
2. Non–English-language
3. Study quality: Does not meet USPSTF criteria for quality
4. Age <18 y unless adult data are broken out separately
5. Study disease definition does not meet our definition of disease (see 2 below)
6. Design: Case study, editorial, letter, case series with <20 patients, review
7. Does not report relevant outcomes
8. Not phlebotomy treatment
9. Mediterranean populations

Inclusion criteria

1. Population: Adults ≥ age 18 y, population applicable to United States (United States, Europe, Australia, New Zealand, Canada), primary iron overload
2. Disease: Meets our disease definition (liver fibrosis, cirrhosis, hepatic failure, hepatocellular carcinoma, diabetes mellitus, cardiomyopathy, or arthropathy attributable to iron overload)
3. Outcomes: Incidence, severity, or progression of clinical hemochromatosis or iron measures, nonspecific symptoms

Key Question 3

Exclusion criteria

1. Nonhuman study
2. Non–English-language
3. Study quality: Does not meet USPSTF criteria for quality
4. Age <18 y unless adult data are broken out separately
5. Study disease definition does not meet our definition of disease (see 2 below)
6. Design: Case series, editorial, letter, review
7. Does not report relevant prevalence or risk measures
8. Does not include original data
9. Not the correct population
10. Excludes Mediterranean populations
11. No *HFE* testing

Inclusion criteria

1. Population: Adults ≥ age 18 y, population applicable to United States (United States, Europe, Australia, New Zealand, Canada)
2. Disease: Meets our disease definition (liver fibrosis, cirrhosis, hepatic failure, hepatocellular carcinoma, diabetes mellitus, cardiomyopathy, or arthropathy attributable to iron overload)
3. Design: cohort, case–control, or cross-sectional study
4. Prevalence or incidence of hemochromatosis or risk for developing hemochromatosis

* USPSTF = U.S. Preventive Services Task Force.

Appendix Table 3. U.S. Preventive Services Task Force Hierarchy of Research Design and Quality Rating Criteria*

Hierarchy of Research Design

I: Properly conducted randomized, controlled trial
II-1: Well-designed controlled trial without randomization
II-2: Well-designed cohort or case–control analytic study
II-3: Multiple time series with or without the intervention; dramatic results from uncontrolled experiments
III: Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

Design-Specific Criteria

Systematic reviews

Criteria
- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance are especially important for systematic reviews

Case–control studies

Criteria
- Accurate ascertainment of case-patients
- Nonbiased selection of case-patients/controls with exclusion criteria applied equally to both

Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Randomized, controlled trials and cohort studies

Criteria
- Initial assembly of comparable groups
  - For randomized, controlled trials: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of the interventions
- All important outcomes considered

Diagnostic accuracy studies

Criteria
- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate result in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test

* Obtained from reference 67.

Appendix Table 4. Studies Excluded from Key Question 1

Study Citation	Reason for Exclusion
Iron overload disorders among Hispanics—San Diego, California, 1995. MMWR Morb Mortal Wkly Rep. 1996;45:991-3. [PMID: 9005307]	Study disease definition does not meet our definition of asymptomatic primary iron overload or clinical disease
A simple genetic test identifies 90% of UK patients with haemochromatosis. The UK Haemochromatosis Consortium. Gut. 1997;41:841-4. [PMID: 9462220]	Not a screening population
Adams PC, Reboussin DM, Barton JC, McLaren CE, Eckfeldt JH, McLaren GD, et al. Hemochromatosis and iron-overload screening in a racially diverse population. N Engl J Med. 2005;352:1769-78. [PMID: 15858186]	Does not report relevant outcomes
Adams PC. Is there a threshold of hepatic iron concentration that leads to cirrhosis in C282Y hemochromatosis? Am J Gastroenterol. 2001;96:567-9. [PMID: 11232708]	Not a screening population
Adams PC, Deugnier Y, Moirand R, Brissot P. The relationship between iron overload, clinical symptoms, and age in 410 patients with genetic hemochromatosis. Hepatology. 1997;25:162-6. [PMID: 8985284]	Not a screening population
Adams PC, Gregor JC, Kertesz AE, Valberg LS. Screening blood donors for hereditary hemochromatosis: decision analysis model based on a 30-year database. Gastroenterology. 1995;109:177-88. [PMID: 7797016]	Does not contain primary data
Adams PC, Kertesz AE, Valberg LS. Clinical presentation of hemochromatosis: a changing scene. Am J Med. 1991;90:445-9. [PMID: 2012084]	Not a screening population
Adams PC, Speechley M, Kertesz AE. Long-term survival analysis in hereditary hemochromatosis. Gastroenterology. 1991;101:368-72. [PMID: 2065912]	Not a screening population
Adams PC. Hepatic iron in hemochromatosis. Dig Dis Sci. 1990;35:690-2. [PMID: 2344801]	Includes data from patients $<$ 18 y
Ammann RW, Muller E, Bansky J, Schuler G, Hacki WH. High incidence of extrahepatic carcinomas in idiopathic hemochromatosis. Scand J Gastroenterol. 1980;15:733-6. [PMID: 6259710]	Not a screening population
Asberg A, Hveem K, Kruger O, Bjerve KS. Persons with screening-detected haemochromatosis: as healthy as the general population? Scand J Gastroenterol. 2002;37:719-24. [PMID: 12126253]	Study disease definition does not meet our definition of asymptomatic primary iron overload or clinical disease
Asberg A, Hveem K, Thorstensen K, Ellekjter E, Kannelonning K, Fjosne U, et al. Screening for hemochromatosis: high prevalence and low morbidity in an unselected population of 65,238 persons. Scand J Gastroenterol. 2001;36:1108-15. [PMID: 11589387]	Does not include C282Y genotyping in screening sequence
Askari AD, Muir WA, Rosner IA, Moskowitz RW, McLaren GD, Braun WE. Arthritis of hemochromatosis. Clinical spectrum, relation to histocompatibility antigens, and effectiveness of early phlebotomy. Am J Med. 1983;75:957-65. [PMID: 6650551]	Not a screening population
Assy N, Adams PC. Predictive value of family history in diagnosis of hereditary hemochromatosis. Dig Dis Sci. 1997;42:1312-5. [PMID: 9201100]	Study design
Bacon BR, Sadiq SA. Hereditary hemochromatosis: presentation and diagnosis in the 1990s. Am J Gastroenterol. 1997;92:784-9. [PMID: 9149185]	Not a screening population
Baer DM, Simons JL, Staples RL, Rumore GJ, Morton CJ. Hemochromatosis screening in asymptomatic ambulatory men 30 years of age and older. Am J Med. 1995;98:464-8. [PMID: 7733125]	Does not include C282Y genotyping in screening sequence
Balan V, Baldus W, Fairbanks V, Michels V, Burritt M, Klee G. Screening for hemochromatosis: a cost-effectiveness study based on 12,258 patients. Gastroenterology. 1994;107:453-9. [PMID: 8039622]	Does not include C282Y genotyping in screening sequence
Barosi G, Salvaneschi L, Grasso M, Martinetti M, Marchetti M, Bodini U, et al. High prevalence of a screening-detected, HFE-unrelated, mild idiopathic iron overload in Northern Italy. Haematologica. 2002;87:472-8. [PMID: 12010659]	Does not report relevant outcomes
Barton JC, Cheatwood SM, Key TJ, Acton RT. Hemochromatosis detection in a health screening program at an Alabama forest products mill. J Occup Environ Med. 2002;44:745-51. [PMID: 12185795]	Does not report relevant outcomes
Barton JC, Barton NH, Alford TJ. Diagnosis of hemochromatosis probands in a community hospital. Am J Med. 1997;103:498-503. [PMID: 9428833]	Not a screening population
Barton JC, Shih WW, Sawada-Hirai R, Acton RT, Harmon L, Rivers C, et al. Genetic and clinical description of hemochromatosis probands and heterozygotes: evidence that multiple genes linked to the major histocompatibility complex are responsible for hemochromatosis. Blood Cells Mol Dis. 1997;23:135-45; discussion 145a-b. [PMID: 9215758].	Not a screening population
Bassett ML, Halliday JW, Ferris RA, Powell LW. Diagnosis of hemochromatosis in young subjects: predictive accuracy of biochemical screening tests. Gastroenterology. 1984;87:628-33. [PMID: 6745616]	Participants $<$ 18 y included
Bassett ML, Halliday JW, Powell LW. Value of hepatic iron measurements in early hemochromatosis and determination of the critical iron level associated with fibrosis. Hepatology. 1986;6:24-9. [PMID: 3943787]	Does not report relevant outcomes
Bell H, Thordal C, Raknerud N, Hansen T, Bosnes V, Halvorsen R, et al. Prevalence of hemochromatosis among first-time and repeat blood donors in Norway. J Hepatol. 1997;26:272-9. [PMID: 9059946]	Does not include C282Y genotyping in screening sequence
Bell H, Berg JP, Undlien DE, Distante S, Raknerud N, Heier HE, et al. The clinical expression of hemochromatosis in Oslo, Norway. Excessive oral iron intake may lead to secondary hemochromatosis even in HFE C282Y mutation negative subjects. Scand J Gastroenterol. 2000;35:1301-7. [PMID: 11199371]	Not a screening population
Borwein ST, Ghent CN, Flanagan PR, Chamberlain MJ, Valberg LS. Genetic and phenotypic expression of hemochromatosis in Canadians. Clin Invest Med. 1983;6:171-9. [PMID: 6652983]	Does not report relevant outcomes
Bradbear RA, Bain C, Siskind V, Schofield FD, Webb S, Axelsen EM, et al. Cohort study of internal malignancy in genetic hemochromatosis and other chronic nonalcoholic liver diseases. J Natl Cancer Inst. 1985;75:81-4. [PMID: 2989605]	Not a screening population
Bradley LA, Haddow JE, Palomaki GE. Population screening for haemochromatosis: a unifying analysis of published intervention trials. J Med Screen. 1996;3:178-84. [PMID: 9041481]	Review article
Bulaj ZJ, Ajioka RS, Phillips JD, LaSalle BA, Jorde LB, Griffen LM, et al. Disease-related conditions in relatives of patients with hemochromatosis. N Engl J Med. 2000;343:1529-35. [PMID: 11087882]	Quality
Buysschaert M, Paris I, Selvais P, Hermans MP. Clinical aspects of diabetes secondary to idiopathic haemochromatosis in French-speaking Belgium. Diabetes Metab. 1997;23:308-13. [PMID: 9342544]	Case series

Continued on following page

Appendix Table 4—**Continued**

Study Citation	Reason for Exclusion
Cadet E, Capron D, Gallet M, Omanga-Leke ML, Boutignon H, Julier C, et al. Reverse cascade screening of newborns for hereditary haemochromatosis: a model for other late onset diseases? J Med Genet. 2005;42:390-5. [PMID: 15863667]	Includes data from patients < 18 y Cannot separate C282Y homozygotes from C282Y heterozygotes
Cartwright GE, Edwards CQ, Kravitz K, Skolnick M, Amos DB, Johnson A, et al. Hereditary hemochromatosis. Phenotypic expression of the disease. N Engl J Med. 1979;301:175-9. [PMID: 449974]	Does not report relevant outcomes
Cecchetti G, Binda A, Piperno A, Nador F, Fargion S, Fiorelli G. Cardiac alterations in 36 consecutive patients with idiopathic haemochromatosis: polygraphic and echocardiographic evaluation. Eur Heart J. 1991;12:224-30. [PMID: 2044557]	Not a screening population
Cogswell ME, Gallagher ML, Steinberg KK, Caudill PhD SP, Looker AC, Bowman BA, et al. HFE genotype and transferrin saturation in the United States. Genet Med. 2003;5:304-10. [PMID: 12865759]	Study disease definition does not meet our definition of asymptomatic primary iron overload or clinical disease
Crawford DH, Jazwinska EC, Cullen LM, Powell LW. Expression of HLA-linked hemochromatosis in subjects homozygous or heterozygous for the C282Y mutation. Gastroenterology. 1998;114:1003-8. [PMID: 9558290]	Not a screening population
Cundy T, Bomford A, Butler J, Wheeler M, Williams R. Hypogonadism and sexual dysfunction in hemochromatosis: the effects of cirrhosis and diabetes. J Clin Endocrinol Metab. 1989;69:110-6. [PMID: 2732293]	Not a screening population
Deugnier YM, Charalambous P, Le Quilleuc D, Turlin B, Searle J, Brissot P, et al. Preneoplastic significance of hepatic iron-free foci in genetic hemochromatosis: a study of 185 patients. Hepatology. 1993;18:1363-9. [PMID: 7902316]	Not a screening population
Distante S, Berg JP, Lande K, Haug E, Bell H. HFE gene mutation (C282Y) and phenotypic expression among a hospitalised population in a high prevalence area of haemochromatosis. Gut. 2000;47:575-9. [PMID: 10986220]	Inconsistent application of exclusion criteria
Edwards CQ, Griffen LM, Kushner JP. The morbidity of hemochromatosis among clinically unselected homozygotes: preliminary report. Adv Exp Med Biol. 1994;356:303-8. [PMID: 7887235]	Does not report relevant outcomes
Edwards CQ, Griffen LM, Kushner JP. Comparison of stainable liver iron between symptomatic and asymptomatic hemochromatosis homozygotes and their homozygous relatives. Am J Med Sci. 1991;301:44-6. [PMID: 1994729]	Not a screening population
Edwards CQ, Griffen LM, Goldgar D, Drummond C, Skolnick MH, Kushner JP. Prevalence of hemochromatosis among 11,065 presumably healthy blood donors. N Engl J Med. 1988;318:1355-62. [PMID: 3367936]	Does not include C282Y genotyping in screening sequence
Edwards CQ, Cartwright GE, Skolnick MH, Amos DB. Homozygosity for hemochromatosis: clinical manifestations. Ann Intern Med. 1980;93:519-25. [PMID: 7436183]	Does not report relevant outcomes
Elliott R, Lin BP, Dent OF, Tait A, Smith CI. Prevalence of hemochromatosis in a random sample of asymptomatic men. Aust N Z J Med. 1986;16:491-5. [PMID: 3467692]	Does not include C282Y genotyping in screening sequence
Elmberg M, Hultcrantz R, Ekbom A, Brandt L, Olsson S, Olsson R, et al. Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives. Gastroenterology. 2003;125:1733-41. [PMID: 14724826]	Not a screened population
Fargion S, Fracanzani AL, Piperno A, Braga M, D'Alba R, Ronchi G, et al. Prognostic factors for hepatocellular carcinoma in genetic hemochromatosis. Hepatology. 1994;20:1426-31. [PMID: 7982640]	Not a screening population
Fargion S, Mandelli C, Piperno A, Cesana B, Fracanzani AL, Fraquelli M, et al. Survival and prognostic factors in 212 Italian patients with genetic hemochromatosis. Hepatology. 1992;15:655-9. [PMID: 1312985]	Not a screening population
Fiel MI, Schiano TD, Bodenheimer HC, Thung SN, King TW, Varma CR, et al. Hereditary hemochromatosis in liver transplantation. Liver Transpl Surg. 1999;5:50-6. [PMID: 9873093]	Not a screening population
Fleming DJ, Jacques PF, Tucker KL, Massaro JM, D'Agostino RB Sr, Wilson PW, et al. Iron status of the free-living, elderly Framingham Heart Study cohort: an iron-replete population with a high prevalence of elevated iron stores. Am J Clin Nutr. 2001;73:638-46. [PMID: 11237943]	Does not report relevant outcomes
Fletcher LM, Dixon JL, Purdie DM, Powell LW, Crawford DH. Excess alcohol greatly increases the prevalence of cirrhosis in hereditary hemochromatosis. Gastroenterology. 2002;122:281-9. [PMID: 11832443]	Not a screening population
Fox CJ, Cullen DJ, Knuiman MW, Cumpston GN, Divitini ML, Rossi E, et al. Effects of body iron stores and haemochromatosis genotypes on coronary heart disease outcomes in the Busselton health study. J Cardiovasc Risk. 2002;9:287-93. [PMID: 12394323]	Study disease definition does not meet our definition of asymptomatic primary iron overload or clinical disease
Fracanzani AL, Conte D, Fraquelli M, Taioli E, Mattioli M, Losco A, et al. Increased cancer risk in a cohort of 230 patients with hereditary hemochromatosis in comparison to matched control patients with non-iron-related chronic liver disease. Hepatology. 2001;33:647-51. [PMID: 11230745]	Not a screening population
Fracanzani AL, Fargion S, Romano R, Conte D, Piperno A, D'Alba R, et al. Portal hypertension and iron depletion in patients with genetic hemochromatosis. Hepatology. 1995;22:1127-31. [PMID: 7557861]	Not a screening population
Gleeson F, Ryan E, Barrett S, Crowe J. Clinical expression of haemochromatosis in Irish C282Y homozygotes identified through family screening. Eur J Gastroenterol Hepatol. 2004;16:859-63. [PMID: 15316409]	Includes data from patients < 18 y
Hallberg L, Bjorn-Rasmussen E, Jungner I. Prevalence of hereditary haemochromatosis in two Swedish urban areas. J Intern Med. 1989;225:249-55. [PMID: 2723582].	Does not include C282Y genotyping in screening sequence
Halliday JW, Russo AM, Cowlishaw JL, Powell LW. Serum-ferritin in diagnosis of haemochromatosis. A study of 43 families. Lancet. 1977;2:621-4. [PMID: 71445]	Does not report relevant outcomes
Hamilton EB, Bomford AB, Laws JW, Williams R. The natural history of arthritis in idiopathic haemochromatosis: progression of the clinical and radiological features over ten years. Q J Med. 1981;50:321-9. [PMID: 7330169]	Not a screening population
Jackson HA, Carter K, Darke C, Guttridge MG, Ravine D, Hutton RD, et al. HFE mutations, iron deficiency and overload in 10,500 blood donors. Br J Haematol. 2001;114:474-84. [PMID: 11529872]	Study disease definition does not meet our definition of asymptomatic primary iron overload or clinical disease
Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. JAMA. 2004;291:711-7. [PMID: 14871914]	Study design

Appendix Table 4—**Continued**

Study Citation	Reason for Exclusion
Jonsson JJ, Johannesson GM, Sigfusson N, Magnusson B, Thjodleifsson B, Magnusson S. Prevalence of iron deficiency and iron overload in the adult Icelandic population. J Clin Epidemiol. 1991;44:1289-97. [PMID: 1753260]	Does not include C282Y genotyping in screening sequence
Jorquera F, Dominguez A, Diaz-Golpe V, Espinel J, Munoz F, Herrera A, et al. C282Y and H63D mutations of the haemochromatosis gene in patients with iron overload. Rev Esp Enferm Dig. 2001;93:293-302. [PMID: 11488107]	Not a screening population
Karlsson M, Ikkala E, Reunanen A, Takkunen H, Vuori E, Makinen J. Prevalence of hemochromatosis in Finland. Acta Med Scand. 1988;224:385-90. [PMID: 3188989]	Does not include C282Y genotyping in screening sequence
Koefoed P, Dalhoff K, Dissing J, Kramer I, Milman N, Pedersen P, et al. HFE mutations and hemochromatosis in Danish patients admitted for HFE genotyping. Scand J Clin Lab Invest. 2002;62:527-35. [PMID: 12512743]	Not a screening population
Lalouel JM, Le Mignon L, Simon M, Fauchet R, Bourel M, Rao DC, et al. Genetic analysis of idiopathic hemochromatosis using both qualitative (disease status) and quantitative (serum iron) information. Am J Hum Genet. 1985;37:700-18. [PMID: 9556659]	Does not report relevant outcomes
Leggett BA, Halliday JW, Brown NN, Bryant S, Powell LW. Prevalence of haemochromatosis amongst asymptomatic Australians. Br J Haematol. 1990;74:525-30. [PMID: 2346731]	Does not include C282Y genotyping in screening sequence
Lin E, Adams PC. Biochemical liver profile in hemochromatosis. A survey of 100 patients. J Clin Gastroenterol. 1991;13:316-20. [PMID: 2066547]	Not a screening population
Lindmark B, Eriksson S. Regional differences in the idiopathic hemochromatosis gene frequency in Sweden. Acta Med Scand. 1985;218:299-304. [PMID: 4072776]	Does not include C282Y genotyping in screening sequence
Livesey KJ, Wimhurst VL, Carter K, Worwood M, Cadet E, Rochette J, et al. The 16189 variant of mitochondrial DNA occurs more frequently in C282Y homozygotes with haemochromatosis than those without iron loading. J Med Genet. 2004;41:6-10. [PMID: 14729817]	Not a screening population
Mainous AG 3rd, Gill JM, Pearson WS. Should we screen for hemochromatosis? An examination of evidence of downstream effects on morbidity and mortality. Arch Intern Med. 2002;162:1769-74. [PMID: 12153381]	Does not report relevant outcomes
Mainous AG 3rd, King DE, Pearson WS, Garr DR. Is an elevated serum transferrin saturation associated with the development of diabetes? J Fam Pract. 2002;51:933-6. [PMID: 12485546]	Does not include C282Y genotyping in screening sequence
Mainous AG 3rd, Wells B, Carek PJ, Gill JM, Geesey ME. The mortality risk of elevated serum transferrin saturation and consumption of dietary iron. Ann Fam Med. 2004;2:139-44. [PMID: 15083854]	Does not include C282Y genotyping in screening sequence
Mainous AG 3rd, Gill JM, Carek PJ. Elevated serum transferrin saturation and mortality. Ann Fam Med. 2004;2:133-8. [PMID: 15083853]	Does not include C282Y genotyping in screening sequence
Mainous AG 3rd, Gill JM, Everett CJ. Transferrin saturation, dietary iron intake, and risk of cancer. Ann Fam Med. 2005;3:131-7. [PMID: 15798039]	Does not report relevant outcomes
Mathews JL, Williams HJ. Arthritis in hereditary hemochromatosis. Arthritis Rheum. 1987;30:1137-41. [PMID: 3675659]	Ineligible study design
McCune CA, Al-Jader LN, May A, Hayes SL, Jackson HA, Worwood M. Hereditary haemochromatosis: only 1% of adult HFEC282Y homozygotes in South Wales have a clinical diagnosis of iron overload. Hum Genet. 2002;111:538-43. [PMID: 12436244]	Not a screening population
McCune CA, Ravine D, Worwood M, Jackson HA, Evans HM, Hutton D. Screening for hereditary haemochromatosis within families and beyond. Lancet. 2003;362:1897-8. [PMID: 14667749]	Not a screening population Quality
Merryweather-Clarke AT, Worwood M, Parkinson L, Mattock C, Pointon JJ, Shearman JD, et al. The effect of HFE mutations on serum ferritin and transferrin saturation in the Jersey population. Br J Haematol. 1998;101:369-73. [PMID: 9609537]	Does not report relevant outcomes
Milman N, Pedersen P, Steig T, Byg KE, Graudal N, Fenger K. Clinically overt hereditary hemochromatosis in Denmark 1948-1985: epidemiology, factors of significance for long-term survival, and causes of death in 179 patients. Ann Hematol. 2001;80:737-44. [PMID: 11797115]	Quality
Milman N. Iron status markers in hereditary haemochromatosis: distinction between individuals being homozygous and heterozygous for the haemochromatosis allele. Eur J Haematol. 1991;47:292-8. [PMID: 1954989]	Does not report relevant outcomes
Moirand R, Jouanolle AM, Brissot P, Le Gall JY, David V, Deugnier Y. Phenotypic expression of HFE mutations: a French study of 1110 unrelated iron-overloaded patients and relatives. Gastroenterology. 1999;116:372-7. [PMID: 9922318]	Does not report relevant outcomes
Moodie SJ, Ang L, Stenner JM, Finlayson C, Khotari A, Levin GE, et al. Testing for haemochromatosis in a liver clinic population: relationship between ethnic origin, HFE gene mutations, liver histology and serum iron markers. Eur J Gastroenterol Hepatol. 2002;14:223-9. [PMID: 11953685]	Not a screening population
Morrison ED, Brandhagen DJ, Phatak PD, Barton JC, Krawitt EL, El-Serag HB, et al. Serum ferritin level predicts advanced hepatic fibrosis among U.S. patients with phenotypic hemochromatosis. Ann Intern Med. 2003;138:627-33. [PMID: 12693884]	Not a screening population
Mura C, Nousbaum JB, Verger P, Moalic MT, Raguenes O, Mercier AY, et al. Phenotype-genotype correlation in haemochromatosis subjects. Hum Genet. 1997;101:271-6. [PMID: 9439654]	Not a screening population
Nash S, Marconi S, Sikorska K, Naeem R, Nash G. Role of liver biopsy in the diagnosis of hepatic iron overload in the era of genetic testing. Am J Clin Pathol. 2002;118:73-81. [PMID: 12109859]	Not a screening population
Nelson RL, Persky V, Davis F, Becker E. Risk of disease in siblings of patients with hereditary hemochromatosis. Digestion. 2001;64:120-4. [PMID: 11684826]	Quality
Niederau C, Niederau CM, Lange S, Littauer A, Abdel-Jalil N, Maurer M, et al. Screening for hemochromatosis and iron deficiency in employees and primary care patients in Western Germany. Ann Intern Med. 1998;128:337-45. [PMID: 9490593]	Does not include C282Y genotyping in screening sequence
Olsson KS, Eriksson K, Ritter B, Heedman PA. Screening for iron overload using transferrin saturation. Acta Med Scand. 1984;215:105-12. [PMID: 6702489]	Does not include C282Y genotyping in screening sequence

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Appendix Table 4—**Continued**

Study Citation	Reason for Exclusion
Olsson KS, Ritter B, Lundin PM. Liver affection in iron overload studied with serum ferritin and serum aminotransferases. Acta Med Scand. 1985;217:79-84. [PMID: 3976436]	Not a screening population
Olynyk JK, Luxon BA, Britton RS, Bacon BR. Hepatic iron concentration in hereditary hemochromatosis does not saturate or accurately predict phlebotomy requirements. Am J Gastroenterol. 1998;93:346-50. [PMID: 9517637]	Does not report relevant outcomes
Panajotopoulos N, Piperno A, Conte D, Mandelli C, Cesana M, Mercuriali F, et al. HLA typing in 67 Italian patients with idiopathic hemochromatosis and their relatives. Tissue Antigens. 1989;33:431-6. [PMID: 2734773]	Study design
Phatak PD, Sham RL, Raubertas RF, Dunnigan K, O'Leary MT, Braggins C, et al. Prevalence of hereditary hemochromatosis in 16031 primary care patients. Ann Intern Med. 1998;129:954-61. [PMID: 9867748]	Does not include C282Y genotyping in screening sequence
Piperno A, Vergani A, Salvioni A, Trombini P, Vigana M, Riva A, et al. Effects of venesections and restricted diet in patients with the insulin-resistance hepatic iron overload syndrome. Liver Int. 2004;24:471-6. [PMID: 15482345]	Not a screening population
Porto G, Vicente C, Fraga J, da Silva BM, de Sousa M. Importance of establishing appropriate local reference values for the screening of hemochromatosis: a study of three different control populations and 136 hemochromatosis family members. Hemochromatosis Clinical and Research Group. J Lab Clin Med. 1992;119:295-305. [PMID: 1541878]	Includes data from patients < 18 y
Porto G, Vicente C, Teixeira MA, Martins O, Cabeda JM, Lacerda R, et al. Relative impact of HLA phenotype and CD4-CD8 ratios on the clinical expression of hemochromatosis. Hepatology. 1997;25:397-402. [PMID: 9021953]	Not a screening population
Poullis A, Moodie SJ, Ang L, Finlayson CJ, Levin GE, Maxwell JD. Routine transferrin saturation measurement in liver clinic patients increases detection of hereditary haemochromatosis. Ann Clin Biochem. 2003;40:521-7. [PMID: 14503989]	Not a screening population
Powell LW, Summers KM, Board PG, Axelsen E, Webb S, Halliday JW. Expression of hemochromatosis in homozygous subjects. Implications for early diagnosis and prevention. Gastroenterology. 1990;98:1625-32. [PMID: 2338199]	Includes data from patients < 18 y
Poynard T, Mathurin P, Lai CL, Guyader D, Poupon R, Tainturier MH, et al. A comparison of fibrosis progression in chronic liver diseases. J Hepatol. 2003;38:257-65. [PMID: 12586290]	Not a screening population
Press RD, Flora K, Gross C, Rabkin JM, Corless CL. Hepatic iron overload: direct HFE (HLA-H) mutation analysis vs quantitative iron assays for the diagnosis of hereditary hemochromatosis. Am J Clin Pathol. 1998;109:577-84. [PMID: 9576576]	Not a screening population
Rhodes DA, Raha-Chowdhury R, Cox TM, Trowsdale J. Homozygosity for the predominant Cys282Tyr mutation and absence of disease expression in hereditary haemochromatosis. J Med Genet. 1997;34:761-4. [PMID: 9321765]	Does not report relevant outcomes
Roberts AG, Whatley SD, Morgan RR, Worwood M, Elder GH. Increased frequency of the haemochromatosis Cys282Tyr mutation in sporadic porphyria cutanea tarda. Lancet. 1997;349:321-3. [PMID: 9024376]	Does not report relevant outcomes
Rossi E, Henderson S, Chin CY, Olynyk J, Beilby JP, Reed WD, et al. Genotyping as a diagnostic aid in genetic haemochromatosis. J Gastroenterol Hepatol. 1999;14:427-30. [PMID: 10355506]	Not a screening population
Rowe JW, Wands JR, Mezey E, Waterbury LA, Wright JR, Tobin J, et al. Familial hemochromatosis: characteristics of the precirrhotic stage in a large kindred. Medicine (Baltimore). 1977;56:197-211. [PMID: 870791]	Does not report relevant outcomes
Ryan E, Byrnes V, Coughlan B, Flanagan AM, Barrett S, O'Keane JC, et al. Underdiagnosis of hereditary haemochromatosis: lack of presentation or penetration? Gut. 2002;51:108-12. [PMID: 12077102]	Includes data from patients < 18 y
Salonen JT, Tuomainen TP, Kontula K. Role of C282Y mutation in haemochromatosis gene in development of type 2 diabetes in healthy men: prospective cohort study. BMJ. 2000;320:1706-7. [PMID: 10864547]	Does not report relevant outcomes
Scotet V, Merour MC, Mercier AY, Chanu B, Le Faou T, Raguenes O, et al. Hereditary hemochromatosis: effect of excessive alcohol consumption on disease expression in patients homozygous for the C282Y mutation. Am J Epidemiol. 2003;158:129-34. [PMID: 12851225]	Does not report relevant outcomes
Sham RL, Ou CY, Cappuccio J, Braggins C, Dunnigan K, Phatak PD. Correlation between genotype and phenotype in hereditary hemochromatosis: analysis of 61 cases. Blood Cells Mol Dis. 1997;23:314-20. [PMID: 9410475]	Not a screening population
Sham RL, Raubertas RF, Braggins C, Cappuccio J, Gallagher M, Phatak PD. Asymptomatic hemochromatosis subjects: genotypic and phenotypic profiles. Blood. 2000;96:3707-11. [PMID: 11090050]	Not a screening population
Smith BN, Kantrowitz W, Grace ND, Greenberg MS, Patton TJ, Ookubo R, et al. Prevalence of hereditary hemochromatosis in a Massachusetts corporation: is Celtic origin a risk factor? Hepatology. 1997;25:1439-46. [PMID: 9185765]	Does not include C282Y genotyping in screening sequence
Waalen J, Nordestgaard BG, Beutler E. The penetrance of hereditary hemochromatosis. Best Pract Res Clin Haematol. 2005;18:203-20. [PMID: 15737885]	Review article
Wands JR, Rowe JA, Mezey SE, Waterbury LA, Wright JR, Halliday JW, et al. Normal serum ferritin concentrations in precirrhotic hemochromatosis. N Engl J Med. 1976;294:302-5. [PMID: 1246269]	Does not report relevant outcomes
Wiggers P, Dalhoj J, Kiaer H, Ring-Larsen H, Petersen PH, Blaabjerg O, et al. Screening for haemochromatosis: prevalence among Danish blood donors. J Intern Med. 1991;230:265-70. [PMID: 1895049]	Does not include C282Y genotyping in screening sequence
Willis G, Jennings BA, Goodman E, Fellows IW, Wimperis JZ. A high prevalence of HLA-H 845A mutations in hemochromatosis patients and the normal population in eastern England. Blood Cells Mol Dis. 1997;23:288-91. [PMID: 9410472]	Does not report relevant outcomes
Willis G, Wimperis JZ, Lonsdale R, Fellows IW, Watson MA, Skipper LM, et al. Incidence of liver disease in people with HFE mutations. Gut. 2000;46:401-4. [PMID: 10673304]	Does not report relevant outcomes
Willis G, Wimperis JZ, Smith K, Fellows IW, Jennings BA. HFE mutations in the elderly. Blood Cells Mol Dis. 2003;31:240-6. [PMID: 12972032]	Study disease definition does not meet our definition of asymptomatic primary iron overload or clinical disease
Wojcik JP, Speechley MR, Kertesz AE, Chakrabarti S, Adams PC. Natural history of C282Y homozygotes for hemochromatosis. Can J Gastroenterol. 2002;16:297-302. [PMID: 12045778]	Not a screening population Includes data from patients < 18 y
Yamashita C, Adams PC. Natural history of the C282Y homozygote for the hemochromatosis gene (HFE) with a normal serum ferritin level. Clin Gastroenterol Hepatol. 2003;1:388-91. [PMID: 15017658]	Not a screening population

Appendix Table 5. Studies Excluded from Key Question 2

Study Citation	Reason for Exclusion
Adams PC, Kertesz AE, Valberg LS. Rate of iron reaccumulation following iron depletion in hereditary hemochromatosis. Implications for venesection therapy. J Clin Gastroenterol. 1993;16:207-10. [PMID: 8505491]	Does not present relevant outcomes
Adams PC. Factors affecting the rate of iron mobilization during venesection therapy for genetic hemochromatosis. Am J Hematol. 1998;58:16-9. [PMID: 9590143]	Does not present relevant outcomes
Askari AD, Muir WA, Rosner IA, Moskowitz RW, McLaren GD, Braun WE. Arthritis of hemochromatosis. Clinical spectrum, relation to histocompatibility antigens, and effectiveness of early phlebotomy. Am J Med. 1983;75:957-65. [PMID: 6650551]	Quality
Barton JC, Bottomley SS. Iron deficiency due to excessive therapeutic phlebotomy in hemochromatosis. Am J Hematol. 2000;65:223-6. [PMID: 11074539]	< 20 patients
Batey RG, Hussein S, Sherlock S, Hoffbrand AV. The role of serum ferritin in the management of idiopathic haemochromatosis. Scand J Gastroenterol. 1978;13:953-7. [PMID: 725519]	Does not present relevant outcomes
Bodemann HH, Tanzi-Fetta RF, Schroter-Urban H, Volk BA, Keul J, Lohr GW. Ferritin in erythrocytes and plasma of patients with iron overload. Blut. 1985;51:25-31. [PMID: 3848335]	Quality
Candell-Riera J, Lu L, Seres L, Gonzalez JB, Batlle J, Permanyer-Miralda G, et al. Cardiac hemochromatosis: beneficial effects of iron removal therapy. An echocardiographic study. Am J Cardiol. 1983;52:824-9. [PMID: 6624673]	Quality
Cesana M, Mandelli C, Tiribelli C, Bianchi PA, Conte D. Concomitant primary hemochromatosis and beta-thalassemia trait: iron depletion by erythrocytapheresis and desferrioxamine. Am J Gastroenterol. 1989;84:150-2. [PMID: 2916524]	< 20 patients
Chow LH, Frei JV, Hodsman AB, Valberg LS. Low serum 25-hydroxyvitamin D in hereditary hemochromatosis: relation to iron status. Gastroenterology. 1985;88:865-9. [PMID: 3838288]	Quality
Cleton MI, de Bruijn WC, van Blokland WT, Marx JJ, Roelofs JM, Rademakers LH. Iron content and acid phosphatase activity in hepatic parenchymal lysosomes of patients with hemochromatosis before and after phlebotomy treatment. Ultrastruct Pathol. 1988;12:161-74. [PMID: 3363682]	< 20 patients
Cleton MI, Roelofs JM, Blok-Van Hoek CJ, De Bruijn WC. Integrated image and X-ray microanalysis of hepatic lysosomes in a patient with idiopathic hemosiderosis before and after treatment by phlebotomy. Scan Electron Microsc. 1986:999-1006. [PMID: 3798023]	< 20 patients
Conte D, Mandelli C, Cesana M, Ferrini R, Marconi M, Bianchi A. Effectiveness of erythrocytapheresis in idiopathic hemochromatosis. Report of 14 cases. Int J Artif Organs. 1989;12:59-62. [PMID: 2925263]	Does not report relevant outcomes
Conte D, Piperno A, Mandelli C, Fargion S, Cesana M, Brunelli L, et al. Clinical, biochemical and histological features of primary haemochromatosis: a report of 67 cases. Liver. 1986;6:310-5. [PMID: 3023781]	Quality
Cundy T, Butler J, Bomford A, Williams R. Reversibility of hypogonadotrophic hypogonadism associated with genetic haemochromatosis. Clin Endocrinol (Oxf). 1993;38:617-20. [PMID: 8334747]	< 20 patients
Dabestani A, Child JS, Henze E, Perloff JK, Schon H, Figueroa WG, et al. Primary hemochromatosis: anatomic and physiologic characteristics of the cardiac ventricles and their response to phlebotomy. Am J Cardiol. 1984;54:153-9. [PMID: 6741807]	< 20 patients
Dymock IW, Cassar J, Pyke DA, Oakley WG, Williams R. Observations on the pathogenesis, complications and treatment of diabetes in 115 cases of haemochromatosis. Am J Med. 1972;52:203-10. [PMID: 5058506]	Quality
Easley RM Jr, Schreiner BF Jr, Yu PN. Reversible cardiomyopathy associated with hemochromatosis. N Engl J Med. 1972;287:866-7. [PMID: 5071966]	< 20 patients
Failla M, Giannattasio C, Piperno A, Vergani A, Grappiolo A, Gentile G, et al. Radial artery wall alterations in genetic hemochromatosis before and after iron depletion therapy. Hepatology. 2000;32:569-73. [PMID: 10960451]	< 20 patients
Fargion S, Mandelli C, Piperno A, Cesana B, Fracanzani AL, Fraquelli M, et al. Survival and prognostic factors in 212 Italian patients with genetic hemochromatosis. Hepatology. 1992;15:655-9. [PMID: 1312985]	Quality
Feely J, Counihan TB. Haemochromatosis presenting as angina and responding to venesection. Br Med J. 1977;2:681-2. [PMID: 902053]	< 20 patients
Fellows IW, Stewart M, Jeffcoate WJ, Smith PG, Toghill PJ. Hepatocellular carcinoma in primary haemochromatosis in the absence of cirrhosis. Gut. 1988;29:1603-6. [PMID: 2850272]	< 20 patients
Fracanzani AL, Fargion S, Romano R, Conte D, Piperno A, D'Alba R, et al. Portal hypertension and iron depletion in patients with genetic hemochromatosis. Hepatology. 1995;22:1127-31. [PMID: 7557861]	Quality
Gama R, Smith MJ, Wright J, Marks V. Hypopituitarism in primary haemochromatosis; recovery after iron depletion. Postgrad Med J. 1995;71:297-8. [PMID: 7596937]	< 20 patients
Goh J, Callagy G, McEntee G, O'Keane JC, Bomford A, Crowe J. Hepatocellular carcinoma arising in the absence of cirrhosis in genetic haemochromatosis: three case reports and review of literature. Eur J Gastroenterol Hepatol. 1999;11:915-9. [PMID: 10514128]	< 20 patients
Grima KM. Therapeutic apheresis in hematological and oncological diseases. J Clin Apher. 2000;15:28-52. [PMID: 10767050]	Review article
Guillygomarc'h A, Mendler MH, Moirand R, Laine F, Quentin V, David V, et al. Venesection therapy of insulin resistance-associated hepatic iron overload. J Hepatol. 2001;35:344-9. [PMID: 11592595]	Wrong population
Hash RB. Hereditary hemochromatosis. J Am Board Fam Pract. 2001;14:266-73. [PMID: 11458969]	Review article
Hines C Jr, Davis WD Jr, Ferrante WA. Hepatoma developing in hemochromatosis in spite of adequate treatment by multiple phlebotomies. Am J Dig Dis. 1971;16:349-55. [PMID: 4324431]	Case report
Hramiak IM, Finegood DT, Adams PC. Factors affecting glucose tolerance in hereditary hemochromatosis. Clin Invest Med. 1997;20:110-8. [PMID: 9088667]	Quality
Hultcrantz R, Angelin B, Bjorn-Rasmussen E, Ewerth S, Einarsson K. Biliary excretion of iron and ferritin in idiopathic hemochromatosis. Gastroenterology. 1989;96:1539-45. [PMID: 2714579]	Quality
Jakeman A, Thompson T, McHattie J, Lehotay DC. Sensitive method for nontransferrin-bound iron quantification by graphite furnace atomic absorption spectrometry. Clin Biochem. 2001;34:43-7. [PMID: 11239514]	< 20 patients
Kaltwasser JP, Werner E, Schalk K, Hansen C, Gottschalk R, Seidl C. Clinical trial on the effect of regular tea drinking on iron accumulation in genetic haemochromatosis. Gut. 1998;43:699-704. [PMID: 9824354]	Quality
Kelly TM, Edwards CQ, Meikle AW, Kushner JP. Hypogonadism in hemochromatosis: reversal with iron depletion. Ann Intern Med. 1984;101:629-32. [PMID: 6435491]	Does not present relevant outcomes
Kohan A, Niborski R, Daruich J, Rey J, Bastos F, Amerise G, et al. Erythrocytapheresis with recombinant human erythropoietin in hereditary hemochromatosis therapy: a new alternative. Vox Sang. 2000;79:40-5. [PMID: 10971213]	< 20 patients

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Appendix Table 5—**Continued**

Study Citation	Reason for Exclusion
Leitman SF, Browning JN, Yau YY, Mason G, Klein HG, Conry-Cantilena C, et al. Hemochromatosis subjects as allogeneic blood donors: a prospective study. Transfusion. 2003;43:1538-44. [PMID: 14617312]	Does not report relevant outcomes
Limdi JK, Crampton JR. Hereditary haemochromatosis. QJM. 2004;97:315-24. [PMID: 15152104]	Review article
Lombard M, Bomford A, Hynes M, Naoumov NV, Roberts S, Crowe J, et al. Regulation of the hepatic transferrin receptor in hereditary hemochromatosis. Hepatology. 1989;9:1-5. [PMID: 2642288]	Does not present relevant outcomes
Lufkin EG, Baldus WP, Bergstralh EJ, Kao PC. Influence of phlebotomy treatment on abnormal hypothalamic-pituitary function in genetic hemochromatosis. Mayo Clin Proc. 1987;62:473-9. [PMID: 3106726]	Quality
Mainous AG 3rd, Wells B, Carek PJ, Gill JM, Geesey ME. The mortality risk of elevated serum transferrin saturation and consumption of dietary iron. Ann Fam Med. 2004;2:139-44. [PMID: 15083854]	No phlebotomy treatment
Mandelli C, Cesarini L, Piperno A, Fargion S, Fracanzani AL, Barisani D, et al. Saturability of hepatic iron deposits in genetic hemochromatosis. Hepatology. 1992;16:956-9. [PMID: 1398502]	Does not present relevant outcomes
McDonnell SM, Witte DL, Cogswell ME, McIntyre R. Strategies to increase detection of hemochromatosis. Ann Intern Med. 1998;129:987-92. [PMID: 9867752]	Review article
Milman N, Pedersen P, ˜Aj Steig T, Byg KE, Graudal N, Fenger K. Clinically overt hereditary hemochromatosis in Denmark 1948-1985: epidemiology, factors of significance for long-term survival, and causes of death in 179 patients. Ann Hematol. 2001;80:737-44. [PMID: 11797115]	Quality
Milman N. Hereditary haemochromatosis in Denmark 1950-1985. Clinical, biochemical and histological features in 179 patients and 13 preclinical cases. Dan Med Bull. 1991;38:385-93. [PMID: 1914539]	Does not report relevant outcomes
Moirand R, Adams PC, Bicheler V, Brissot P, Deugnier Y. Clinical features of genetic hemochromatosis in women compared with men. Ann Intern Med. 1997;127:105-10. [PMID: 9229998]	Does not report relevant outcomes
Morcos M, Dubois S, Bralet MP, Belghiti J, Degott C, Terris B. Primary liver carcinoma in genetic hemochromatosis reveals a broad histologic spectrum. Am J Clin Pathol. 2001;116:738-43. [PMID: 11710692]	Does not report relevant outcomes
Muncunill J, Vaquer P, Galmes A, Obrador A, Parera M, Bargay J, et al. In hereditary hemochromatosis, red cell apheresis removes excess iron twice as fast as manual whole blood phlebotomy. J Clin Apher. 2002;17:88-92. [PMID: 12210712]	< 20 patients
Muting D, Kalk JF, Fischer R, Wiewel D. Spontaneous regression of oesophageal varices after long-term conservative treatment. Retrospective study in 20 patients with alcoholic liver cirrhosis, posthepatitic cirrhosis and haemochromatosis with cirrhosis. J Hepatol. 1990;10:158-62. [PMID: 2332585]	Not phlebotomy treatment
Niederau C, Stremmel W, Strohmeyer GW. Clinical spectrum and management of haemochromatosis. Baillieres Clin Haematol. 1994;7:881-901. [PMID: 7881158]	Review article
Niederau C, Strohmeyer G, Stremmel W. Epidemiology, clinical spectrum and prognosis of hemochromatosis. Adv Exp Med Biol. 1994;356:293-302. [PMID: 7887234]	Review article
Olsson KS, Ritter B, Lundin PM. Liver affection in iron overload studied with serum ferritin and serum aminotransferases. Acta Med Scand. 1985;217:79-84. [PMID: 3976436]	Quality
Piperno A, Vergani A, Salvioni A, Trombini P, Vigano M, Riva A, et al. Effects of venesections and restricted diet in patients with the insulin-resistance hepatic iron overload syndrome. Liver Int. 2004;24:471-6. [PMID: 15482345]	Does not report relevant outcomes
Propper R, Nathan D. Clinical removal of iron. Annu Rev Med. 1982;33:509-19. [PMID: 6282184]	Clinical review article
Prunescu CC, Prunescu P, Vilcu AL. Ultrastructure of the liver in idiopathic haemosiderosis and results of a treatment by repeated bleedings. Morphol Embryol (Bucur). 1987;33:133-6. [PMID: 2956507]	Case report
Riquelme A, Soza A, Nazal L, Martinez G, Kolbach M, Patillo A, et al. Histological resolution of steatohepatitis after iron depletion. Dig Dis Sci. 2004;49:1012-5. [PMID: 15309893]	Case report
Sargent T, Saito H, Winchell HS. Iron absorption in hemochromatosis before and after phlebotomy therapy. J Nucl Med. 1971;12:660-7. [PMID: 5000107]	Does not report relevant outcomes
Seamark CJ, Hutchinson M. Controversy in primary care: Should asymptomatic haemochromatosis be treated? BMJ. 2000;320:1314-7. [PMID: 10807626]	Case report
Sigal SH, Fleischner GM, Weiner FR. Hypogonadal-induced anemia in genetic hemochromatosis: implications for phlebotomy therapy. Am J Gastroenterol. 1995;90:152-3. [PMID: 7801923]	Case report
Spellberg MA. Treatment of hemochromatosis. Am J Gastroenterol. 1969;51:516-22. [PMID: 4894612]	Review article
Tiniakos G, Williams R. Cirrhotic process, liver cell carcinoma and extrahepatic malignant tumors in idiopathic haemochromatosis. Study of 71 patients treated with venesection therapy. Appl Pathol. 1988;6:128-38. [PMID: 2839215]	Quality
Weintraub LR, Conrad ME, Crosby WH. The treatment of hemochromatosis by phlebotomy. Med Clin North Am. 1966;50:1579-90. [PMID: 5339192]	< 20 patients

Appendix Table 6. Studies Excluded from Key Question 3

Study Citation	Reason for Exclusion
Adams PC, Agnew S. Alcoholism in hereditary hemochromatosis revisited: prevalence and clinical consequences among homozygous siblings. Hepatology. 1996;23:724-7. [PMID: 8666324]	Case series
Adams PC, Kertesz AE, Valberg LS. Clinical presentation of hemochromatosis: a changing scene. Am J Med. 1991;90:445-9. [PMID: 2012084]	Case series
Adams PC, Kertesz AE, Valberg LS. Screening for hemochromatosis in children of homozygotes: prevalence and cost-effectiveness. Hepatology. 1995;22:1720-7. [PMID: 7489980]	<18 y included
Adams PC. Haemochromatosis: find them or forget about them? Eur J Gastroenterol Hepatol. 2004;16:857-8. [PMID: 15316408]	Editorial
Assy N, Adams PC. Predictive value of family history in diagnosis of hereditary hemochromatosis. Dig Dis Sci. 1997;42:1312-5. [PMID: 9201100]	No *HFE* testing
Bacon BR, Olynyk JK, Brunt EM, Britton RS, Wolff RK. HFE genotype in patients with hemochromatosis and other liver diseases. Ann Intern Med. 1999;130:953-62. [PMID: 10383365]	Does not meet our definition of clinical hemochromatosis
Bassett ML, Halliday JW, Ferris RA, Powell LW. Diagnosis of hemochromatosis in young subjects: predictive accuracy of biochemical screening tests. Gastroenterology. 1984;87:628-33. [PMID: 6745616]	Does not include primary results
Bassett ML, Halliday JW, Powell LW. Value of hepatic iron measurements in early hemochromatosis and determination of the critical iron level associated with fibrosis. Hepatology. 1986;6:24-9. [PMID: 3943787]	Case series
Bhavnani M, Lloyd D, Bhattacharyya A, Marples J, Elton P, Worwood M. Screening for genetic haemochromatosis in blood samples with raised alanine aminotransferase. Gut. 2000;46:707-10. [PMID: 10764716]	Quality
Bonkovsky HL, Jawaid Q, Tortorelli K, LeClair P, Cobb J, Lambrecht RW, et al. Non-alcoholic steatohepatitis and iron: increased prevalence of mutations of the HFE gene in non-alcoholic steatohepatitis. J Hepatol. 1999;31:421-9. [PMID: 10488699]	Does not meet our definition of clinical hemochromatosis
Bregman H, Gelfand MC, Winchester JF, Manz HJ, Knepshield JH, Schreiner GE. iron-overload-associated myopathy in patients on maintenance haemodialysis: a histocompatibility-linked disorder. Lancet. 1980;2:882-5. [PMID: 6107546]	Not the correct population
Brissot P, Moirand R, Jouanolle AM, Guyader D, Le Gall JY, Deugnier Y, et al. A genotypic study of 217 unrelated probands diagnosed as "genetic hemochromatosis" on "classical" phenotypic criteria. J Hepatol. 1999;30:588-93. [PMID: 10207799]	Does not report relevant prevalence or risk measures
Campo S, Restuccia T, Villari D, Raffa G, Cucinotta D, Squadrito G, et al. Analysis of haemochromatosis gene mutations in a population from the Mediterranean Basin. Liver. 2001;21:233-6. [PMID: 11454185]	Not the correct population
Cavanaugh JA, Wilson SR, Bassett ML. Genetic testing for HFE hemochromatosis in Australia: the value of testing relatives of simple heterozygotes. J Gastroenterol Hepatol. 2002;17:800-3. [PMID: 12121511]	Does not include primary results
Conte D, Manachino D, Colli A, Guala A, Aimo G, Andreoletti M, et al. Prevalence of genetic hemochromatosis in a cohort of Italian patients with diabetes mellitus. Ann Intern Med. 1998;128:370-3. [PMID: 9490597]	Not the correct population
Dalury DF, Ewald FC, Christie MJ, Scott RD. Total knee arthroplasty in a group of patients less than 45 years of age. J Arthroplasty. 1995;10:598-602. [PMID: 9273369]	Does not report relevant prevalence or risk measures
Ellervik C, Mandrup-Poulsen T, Nordestgaard BG, Larsen LE, Appleyard M, Frandsen M, et al. Prevalence of hereditary haemochromatosis in late-onset type 1 diabetes mellitus: a retrospective study. Lancet. 2001;358:1405-9. [PMID: 11705485]	Not the correct population
Feller ER, Pont A, Wands JR, Carter EA, Foster G, Kourides IA, et al. Familial hemochromatosis. Physiologic studies in the precirrhotic stage of the disease. N Engl J Med. 1977;296:1422-6. [PMID: 194151]	Case series
Fiel MI, Schiano TD, Bodenheimer HC, Thung SN, King TW, Varma CR, et al. Hereditary hemochromatosis in liver transplantation. Liver Transpl Surg. 1999;5:50-6. [PMID: 9873093]	Does not report relevant prevalence or risk measures
Gleeson F, Ryan E, Barrett S, Crowe J. Clinical expression of haemochromatosis in Irish C282Y homozygotes identified through family screening. Eur J Gastroenterol Hepatol. 2004;16:859-63. [PMID: 15316409]	Does not report relevant prevalence or risk measures
Guyader D, Jacquelinet C, Moirand R, Turlin B, Mendler MH, Chaperon J, et al. Noninvasive prediction of fibrosis in C282Y homozygous hemochromatosis. Gastroenterology. 1998;115:929-36. [PMID: 9753496]	Not the correct population
Hultcrantz R, Gabrielsson N. Patients with persistent elevation of aminotransferases: investigation with ultrasonography, radionuclide imaging and liver biopsy. J Intern Med. 1993;233:7-12. [PMID: 8429291]	Not relevant outcomes
Jeffrey GP, Adams PC. Pitfalls in the genetic diagnosis of hereditary hemochromatosis. Genet Test. 2000;4:143-6. [PMID: 10953953]	Editorial
Jordan JM. Arthritis in hemochromatosis or iron storage disease. Curr Opin Rheumatol. 2004;16:62-6. [PMID: 14673391]	Review article
Jorquera F, Dominguez A, Diaz-Golpe V, Espinel J, Munoz F, Herrera A, et al. C282Y and H63D mutations of the haemochromatosis gene in patients with iron overload. Rev Esp Enferm Dig. 2001;93:293-302. [PMID: 11488107]	Does not report relevant prevalence or risk measures
Koefoed P, Dalhoff K, Dissing J, Kramer I, Milman N, Pedersen P, et al. HFE mutations and hemochromatosis in Danish patients admitted for HFE genotyping. Scand J Clin Lab Invest. 2002;62:527-35. [PMID: 12512743]	Quality
Krawczak M, Cooper DN, Schmidtke J. Estimating the efficacy and efficiency of cascade genetic screening. Am J Hum Genet. 2001;69:361-70. [PMID: 11431707]	Does not include primary results
Li J, Zhu Y, Singal DP. HFE gene mutations in patients with rheumatoid arthritis. J Rheumatol. 2000;27:2074-7. [PMID: 10990216]	Quality
Mathews JL, Williams HJ. Arthritis in hereditary hemochromatosis. Arthritis Rheum. 1987;30:1137-41. [PMID: 3675659]	Not *HFE*
McCune CA, Ravine D, Worwood M, Jackson HA, Evans HM, Hutton D. Screening for hereditary haemochromatosis within families and beyond. Lancet. 2003;362:1897-8. [PMID: 14667749]	Does not report relevant prevalence or risk measures
Nassar BA, Zayed EM, Title LM, O'Neill BJ, Bata IR, Kirkland SA, et al. Relation of HFE gene mutations, high iron stores and early onset coronary artery disease. Can J Cardiol. 1998;14:215-20. [PMID: 9520858]	Quality
Nelson RL, Persky V, Davis F, Becker E. Risk of disease in siblings of patients with hereditary hemochromatosis. Digestion. 2001;64:120-4. [PMID: 11684826]	Quality
Olynyk J, Hall P, Ahern M, Kwiatek R, Mackinnon M. Screening for genetic haemochromatosis in a rheumatology clinic. Aust N Z J Med. 1994;24:22-5. [PMID: 8002853]	Quality

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Appendix Table 6—**Continued**

Study Citation	Reason for Exclusion
Panajotopoulos N, Piperno A, Conte D, Mandelli C, Cesana M, Mercuriali F, et al. HLA typing in 67 Italian patients with idiopathic hemochromatosis and their relatives. Tissue Antigens. 1989;33:431-6. [PMID: 2734773]	Not the correct population
Peterlin B, Globocnik Petrovic M, Makuc J, Hawlina M, Petrovic D. A hemochromatosis-causing mutation C282Y is a risk factor for proliferative diabetic retinopathy in Caucasians with type 2 diabetes. J Hum Genet. 2003;48:646-9. [PMID: 14618419]	Not the correct population
Piperno A, D'Alba R, Fargion S, Roffi L, Sampietro M, Parma S, et al. Liver iron concentration in chronic viral hepatitis: a study of 98 patients. Eur J Gastroenterol Hepatol. 1995;7:1203-8. [PMID: 8789313]	Not the correct population
Rasmussen ML, Folsom AR, Catellier DJ, Tsai MY, Garg U, Eckfeldt JH. A prospective study of coronary heart disease and the hemochromatosis gene (HFE) C282Y mutation: the Atherosclerosis Risk in Communities (ARIC) study. Atherosclerosis. 2001;154:739-46. [PMID: 11257277]	Does not report relevant prevalence or risk measures
Roberts AG, Whatley SD, Morgan RR, Worwood M, Elder GH. Increased frequency of the haemochromatosis Cys282Tyr mutation in sporadic porphyria cutanea tarda. Lancet. 1997;349:321-3. [PMID: 9024376]	Does not meet our definition of clinical hemochromatosis
Rosenqvist M, Hultcrantz R. Prevalence of a haemochromatosis among men with clinically significant bradyarrhythmias. Eur Heart J. 1989;10:473-8. [PMID: 2788086]	No *HFE* testing
Sampietro M, Piperno A, Lupica L, Arosio C, Vergani A, Corbetta N, et al. High prevalence of the His63Asp HFE mutation in Italian patients with porphyria cutanea tarda. Hepatology. 1998;27:181-4. [PMID: 9425935]	Does not meet our definition of clinical hemochromatosis
Schmid H, Struppler C, Braun GS, Kellner W, Kellner H. Ankle and hindfoot arthropathy in hereditary hemochromatosis. J Rheumatol. 2003;30:196-9. [PMID: 12508413]	Not the correct population
Sham RL, Raubertas RF, Braggins C, Cappuccio J, Gallagher M, Phatak PD. Asymptomatic hemochromatosis subjects: genotypic and phenotypic profiles. Blood. 2000;96:3707-11. [PMID: 11090050]	Not the correct population
Shoaf EH Jr. Hemochromatosis discovered through blood donor screening for alanine aminotransferase. N C Med J. 1990;51:443-5. [PMID: 2234109]	Case report
Siezenga MA, Rasp E, Wijermans PW. Testing families with HFE-related hereditary haemochromatosis. Neth J Med. 2004;62:156-9. [PMID: 15366698]	Case report
Simon M, Alexandre JL, Bourel M, Le Marec B, Scordia C. Heredity of idiopathic haemochromatosis: a study of 106 families. Clin Genet. 1977;11:327-41. [PMID: 862210]	Quality
Tannapfel A, Stolzel U, Kostler E, Melz S, Richter M, Keim V, et al. C282Y and H63D mutation of the hemochromatosis gene in German porphyria cutanea tarda patients. Virchows Arch. 2001;439:1-5. [PMID: 11499833]	Does not meet our definition of clinical hemochromatosis
Timms AE, Sathananthan R, Bradbury L, Athanasou NA, Wordsworth BP, Brown MA. Genetic testing for haemochromatosis in patients with chondrocalcinosis. Ann Rheum Dis. 2002;61:745-7. [PMID: 12117686]	Quality

Appendix Table 7. **Longitudinal Studies of Disease Development in C282Y Homozygotes***

Study, Year (Reference)	Population	Criteria/Sequence and Results for Screening†	Criteria and Results for Iron Overload†	Definition and Results for Morbidity	Quality
Olynyk et al., 2004 (46)	Retrospective examination of 3011 randomly selected participants (age 20–79 y) from Busselton, Australia, cohort genotyped in 1998 Available data from 1981, 1994, and 1998	*HFE* genotype 16 of 3011 C282YY homozygotes, 4 previously diagnosed and undergoing TP (those 4 were excluded) Serum available for 10 of 12 patients Elevated iron measures 1981: 3 of 9 Median age: 30 y 1994: 9 of 10 Median age: 43 y 1998: 10 of 10 Median age: 47 y SF level > 300 μg/L 1981: 5 of 10 1994: 5 of 10 (4 of 5 were same as 1981) 1998: 6 of 10	> 90 μmol/g 5 of 6 had biopsy in 1998 Possible iron overload Men: 4 of 4 (calculated) with TS > 0.50 and SF level > 300 μg/L Women: 2 of 6 (calculated) with TS > 0.45 and SF level > 200 μg/L	Fibrosis (6 had biopsy): 2 of 6 Cirrhosis: 1 of 6 (cirrhotic patient drank > 6 alcoholic drinks/day) Diabetes: 1 patient at age 19 y; thought to be unrelated to HC Arthralgia: 4 of 10	Good—potential for selective mortality bias, but effect appears to have been minimal because of reasonably complete follow-up of cohort (85%). Very small sample; not all patients were of the age at which disease expression would be expected (i.e., women ≥ 50 y).
Andersen et al., 2004 (47)	Retrospective cohort from Copenhagen Heart Study, 1976–2001; *n* = 9174 White persons > 99% 47% (9174 of 19 698) of original Copenhagen study sample	*HFE* genotype C282Y:C282Y 23 of 9174 20 still alive TS > 0.50 in 2001 Men: 5 of 7, women: 13 of 16 SF level > 250 μg/L in 2001 Men: 6 of 7 SF level > 200 μg/L in 2001 Women: 10 of 16 Iron measure progression (1976–2001) Mean TS Women Mean age, 25 y: 0.50 Mean age, 85 y: 0.70 Men Mean age, 35 y: 0.70 Mean age, 80 y: 0.80 Mean SF level Women Mean age, 25 y: 120 μg/L Mean age, 85 y: 500 μg/L Men Mean age, 35 y: 800 μg/L Mean age, 80 y: 400 μg/L	Possible iron overload Men: TS > 0.50, SF level > 300 μg/L, and CE: 5 of 7 (calculated) Women: TS > −0.45, SF level > 200 μg/L, and CE: 9 of 16 (calculated) Liver biopsies not done	Diabetes: 1 of 23 (4%) Liver disease: 0 of 23 (0%) (Defined by AST level > 50 U/L; alkaline phosphatase level > 275 U/L; coagulation tests < 70%; bilirubin level > 17) Clinical work-ups in 2001 for liver disease, hypogonadism, cardiomyopathy: 0 of 23 Work-up for arthralgias: 2 of 23 Subclinical HC: 1 of 23	Fair—results may be compromised by selective mortality bias due to large attrition of the cohort. No liver biopsies to confirm disease expression or iron overload.

* AST = aspartate aminotransferase; C282YY = C282Y/C282Y; HC = hemochromatosis; SF = serum ferritin; TP = therapeutic phlebotomy; TS = transferrin saturation.
† Criteria defined in Table 2.

Appendix Table 8. Genotype Screening Studies in Various Populations*

Study, Year (Reference)	Population	C282Y:C282Y Frequency	TS† (Initial Test Unless Stated)	SF†	Iron Overload	Diabetes	Elevated Liver Enzyme Levels	Hepatic Fibrosis or Cirrhosis	Quality
Health clinics									
Beutler et al., 2002a (32); Beutler et al., 2002b (48), Beutler et al., 2000 (49), Waalen et al., 2002 (50)	KP San Diego *n* = 41 038 Mean age, 57 y Non-Hispanic white persons: 77% 140 C282YY homozygotes from KP San Diego screening study	152 of 41 038 3.7/1000	>0.50: men, 75%; women, 40% Elevated overall: 57% After exclusion of frequent blood donors: 76% men, 41% women	>250 μg/L: men, 76% >200 μg/L: women, 54% Elevated overall: 65% After exclusion of frequent blood donors: men; 77%; women, 56%	NR 102 eligible (not previously treated) 54 completed treatment 13 of 54 (24%) had > 5 g iron removed	C282YY: 5.6% Non-C282YY: 8.4%	AST level > 40 U/L C282YY: 8.2% Non-C282YY: 3.8%	NR	Good—excellent controls. Excluded previously identified C282Y homozygotes in determining prevalence of genotype and disease expression.
Deugnier et al., 2002 (51)	Brittany, France *n* = 9396 35.8% men (deliberately weighted to include younger men)	54 of 9396 5.7/1000	>0.55: men, 80% >0.50: women, 41% Elevated overall: 48%	>280 μg/L: men, 70% >130 μg/L: women, 33% Elevated overall: 40%	NR	Men C282YY: 0% Non-C282YY: 0.8% Women C282YY: 2.3% Non-C282YY: 0.9%	Men ALT level > 70 U/L C282YY: 10% Non-C282YY: 5% Women ALT level > 35 U/L C282YY: 5% Non-C282YY: 5%	Fair—not strictly population-based because overselected. Inclusion of younger men could minimize disease expression.	
Population screening									
Olynyk et al., 1999 (52)	Busselton, Australia *n* = 3011, randomly selected 50% men Predominately white persons Age, 20–79 y	16 of 3011 5.3/1000 4 of 16 previously diagnosed 12 new C282YY (5.3/1000)	>0.45: 93.8% 2nd measurement > 0.45: 93.8%	>300 μg/L: 50% >300 μg/L in untreated persons: 58.3%	Liver biopsy: 7 of 12 (58%) HII > 1.9: 4 of 7 (57.1%) of those having biopsy 33% of C282YY homozygotes HIC> 20 μmol/g dry: 100% of those biopsied (7/7) 58% C282YY	NR	NR	Fibrosis: 29% of persons having biopsy (2 of 7) Cirrhosis: 14% of persons having biopsy (1 of 7) (also had history of alcohol intake >60 g/d) No controls	Good—considered confounders for liver disease. Excluded previously identified C282Y homozygotes.
Voter rolls									
Burt et al., 1998 (53)	*n* = 1064 voters in New Zealand 39.8% men Mean age: 50 y	5 of 1064 4.7/1000	> 0.55: 100%	Second measurement: >300 μg/L: men, 100% >160 μg/L: women, 50% Elevated overall: 60%	Liver biopsy: 60% HII > 1.9: 3 of 3 (100%) selected C282YY homozygotes 3 of 5 (60%) all C282YY homozygotes	NR	NR	NR	Fair—did not exclude previously identified C282Y homozygotes, so estimates of screening prevalence are less accurate. Did not consider confounders for liver disease.
Employment screening									
Distante et al., 1999 (54)	*n* = 505 hospital employees in Oslo, Norway 79% women Mean age: 38 y	2 of 505 4/1000	>0.50: 100%	>200 μg/L: 100%	TP in 50%: 5.2 g of iron removed 1 of 1 with IO by TP HIC: 47 μmol/g Biopsy: 0 of 1 IO: 50% selected C282YY homozygotes Total IO: 100%	NR	NR	NR	Good
McDonnell et al., 1999 (55)	*n* = 1450 HMO employees in Springfield, Missouri 83% women 98% white Mean age: 41 y	6 of 1450 4.1/1000	>0.50: women, 2 >0.60: men, 2 Elevated overall: 67% of C282YY homozygotes	>95th percentile for age and sex: 50% of C282YY homozygotes	HII = 2.2: 1 of 1 by biopsy 1 of 2 by TP 2 of 3 (67%) of selected C282YY homozygotes 2 of 6 (33%) of all C282YY homozygotes	NR	NR	Fibrosis: 0 of 1 (0%)	Fair/good—some inconsistencies between data reported in text and figures/tables. Did not consider confounders for liver disease.

Appendix Table 8—Continued

Study, Year (Reference)	Population	C282Y:C282Y Frequency	TS† (Initial Test Unless Stated)	SF†	Iron Overload	Diabetes	Elevated Liver Enzyme Levels	Hepatic Fibrosis or Cirrhosis	Quality
Delatycki et al., 2005 (56)	*n* = 11 307 workplace employees in Australia 47% men 63% northern European	51 of 11 307 4 previously diagnosed 4.5/1000 47 new C282YY homozygotes	Criteria for elevation not given; 65% had "elevated" values	NR	6 recommended for testing; 4 had biopsy	NR	NR	Fibrosis: 2 of 4 had biopsy 50% of selected C282YY homozygotes 4.3% (2 of 47) of all C282YY homozygotes	Fair—did not exclude previously identified C282Y homozygotes, so estimates of screening prevalence are less accurate. Did not consider confounders for liver disease. Unclear criteria for iron overload.
Family studies									
Barton et al., 1999 (57)	*n* = 150 relatives of 61 probands in Alabama 52% women 100% white Mean age: 46 y 1 patient < 18 y was C282YY homozygote	25/149 161/1000	> 0.50: women, 2 > 0.60: men, 2 Overall: 87.5%	> 300 μg/L (men) > 200 μg/L (women) Elevated overall: 96%	NR	16%	NR	2/25 (8%)	Fair—unable to determine how many tested family members were spouses.
Powell et al., 2006 (58)	401 C282YY first-degree relatives of 259 probands with proven C282YY-associated HC 50% female Mean age: Men, 38 y; Women, 44 y	ND	Men: Mean, 72% (range, 12%–100%) Women: Mean, 64% (range, 7%–100%)	Men: Median, 700 μg/L Women: Median, 300 μg/L	Hepatic stain ≥ 3+: Men Selected C282YY homozygotes: 82 of 111 (74%) All C282YY homozygotes: 82 of 200 (41%) Women Selected C282YY homozygotes: 46 of 74 (62%) All C282YY homozygotes: 46 of 201 (23%)	Men: 4 of 200 (2%) Women: 7 of 201 (3%)	Men: 24% Women: 7%	Fibrosis or cirrhosis: Men Selected C282YY homozygotes: 32 of 111 (29%) All C282YY homozygotes: 32 of 200 (16%) Women Selected C282YY homozygotes: 5 of 74 (7%) All C282YY homozygotes: 5 of 201 (2%)	Fair—large sample with reasonably well-specified diagnostic and case criteria. Sample clearly was selected, but no information provided to judge how selective. May fairly represent family screening-detected, but no information given on number tested or whether some were omitted. Did not represent "asymptomatic" general population screening because all persons who underwent genotyping had some initial elevation in serum iron levels. Very selective group for treatment responsiveness; all those with alcohol intake were omitted.

* ALT = alanine aminotransferase; AST = aspartate aminotransferase; C282YY = C282Y/C282Y; HIC = hepatic iron content; HII = hepatic iron index; HMO = health maintenance organization; IO = iron overload; KP = Kaiser Permanente; ND = not determined; NR = not recorded; SF = serum ferritin; TP = therapeutic phlebotomy.
† In homozygotes.

Appendix Table 9. Therapeutic Phlebotomy Studies for Key Question 2*

Study, Year (Reference)	Setting and Study Design	Population	Inclusion Criteria	Control Group	Follow-up	Treatment	Measure and Results	Adverse Events	Quality
Adams et al., 1991 (25)	Specialty clinic Canada Retrospective case series	*n* = 85 Probands: 48 Discovered family members: 37 Men: 53 Arthritis: 40 Diabetes: 18	Diagnosed between 1958 and 1989 Diagnosis was based on clinical history, physical examination, SF levels, and TS and was confirmed through liver biopsy Patients with iron-loading anemias, transfusional iron overload, and dietary iron overload were excluded	Survival was compared against provincial life-table data matched for age and sex	Mean: 8.1 (SD, 6.8) y Analysis was censored at 20 y because only 5 patients were followed for >20 y	500 mL blood/wk until SF level < 30 μg/L or patient became anemic Mean number of treatments: 43 (SD, 51) Treatment resumed if SF levels became elevated	Deaths: 17 Cumulative survival: 5 y: 87% 10 y: 81% 20 y: 71% Expected survival: significantly decreased survival at all times except 1 y and >14 y No significant difference between noncirrhotic patients and hypothetical cohort of age- and sex-matched patients Adjusted RR for death: Cirrhosis: 5.54 Arthritis: 0.24	NR	Fair
Bomford and Williams, 1976 (59)	Specialty clinic United Kingdom Case series	*n* = 111 Patients diagnosed through routine clinical practice who received treatment Treated: 85 Untreated controls: 26	Excluded persons with secondary iron overload. Diagnosis made "by clinical, biochemical and where possible histological criteria"	26 untreated historical controls who were not comparable to treated patients	1937 to approximately 1975	600 mL was removed weekly until hemoglobin ≤ 10 g/dL and serum iron level decreased to <10 μmol/L Biopsy usually repeated after completion of treatment. Treatment resumed if chelatable body iron levels increased to >1000 μg/kg body weight 79 of 85 completed full course	Diabetes: 56 Improved: 16 of 56 Worsened: 7 of 56 New cases: 3 Liver histology: 75 Improved: 5 of 75 No definite change: 68 of 75 Worsened: 2 of 75	NR	Fair
Niederau et al., 1996 (60)	Diagnosed patients from primary care clinics Germany Retrospective case series	*n* = 251 Mean age: 45.7 (SD, 10.8) y Men: 224 Noncirrhotic: 109 Asymptomatic: 41 Family screening: 15 Cirrhotic: 142 Asymptomatic: 7 Diabetic: 120 2 lost to follow-up	Diagnosed between 1947 and 1991 Patients were diagnosed on basis of clinical features and biochemical test results: liver function, serum iron, TS, and SF. Confirmed by liver biopsy	Expected deaths were calculated for a German normal population that was age- and sex-matched for time period of observation	Mean: 14.1 (SD, 6.8) y	From 1979 on, patients were treated 1–2 times/wk by TP (500 mL) until SF levels were normal 185 patients with documented iron depletion received mean of 84.8 (SD, 4.4) treatments to achieve depletion All patients underwent 4–12 TPs per y after depletion	Cumulative survival: 5 y: 93% 10 y: 77% 20 y: 55% 30 y: 20% Significantly reduced compared with expected survival in matched population Liver iron concentration at diagnosis per fibrosis stage: **Stage / Pts, *n* / Liver Iron (SD), *μmol/g*** 0 / 7 / 11.6 (1.8) 1 / 10 / 13.9 (1.1) 2 / 9 / 16.9 (1.4) 3 / 15 / 22.4 (2.0) All / 41 / 16.1 (1.6) Changes in fibrosis stage after iron depletion: **Stage / I, *n* / W, *n* / U, *n*** 0 / 0 / 1 / 20 1 / 10 / 1 / 21 2 / 20 / 0 / 19 3 / 12 / 0 / 81 **Sign/Symptom / AD, % / I, % / U, % / W, %** Weakness/lethargy / 80 / 55 / 40 / 6 Abdominal pain / 56 / 68 / 29 / 1 Arthralgia / 45 / 30 / 50 / 20 Elevated AST or ALT level / 81 / 73 / 25 / 2 Pigmentation / 68 / 68 / 32 / 0 Loss of potency (163 men) / 40 / 19 / 69 / 12 Electrocardiographic changes / 35 / 34 / 61 / 5 Diabetes mellitus / 44 / 41 / 53 / 6 Impaired glucose tolerance / 15 / 37 / 56 / 7	NR	Fair–poor

Appendix Table 9—**Continued**

Study, Year (Reference)	Setting and Study Design	Population	Inclusion Criteria	Control Group	Follow-up	Treatment	Measure and Results	Adverse Events	Quality
McDonnell et al., 1999 (55)	Population-based mailings to all known patients with HC and organizations with access to patients with HC in United States, Canada, Australia, and northern Europe Patients from ≥17 countries, including United States (84%), Australia (6%), United Kingdom (6%), and Canada (4%) Retrospective cross-sectional study	*n* = 2851 patients (80% of all surveys mailed) White: 99% Men: 62% Diagnosis made 1990 or later: 70% Diagnosis made before 1980: 6%	Led to diagnosis: 35% from symptoms related to hereditary HC, 45% from routine or ancillary laboratory test, 20% from diagnosis of family member 56% diagnosed by primary care physician 67% initially diagnosed with alternate condition to explain symptoms Mean age at symptom onset: 41 (SD, 14) y Mean age when sought treatment: 43 (SD, 14) y Mean age at diagnosis: 50 (SD, 13) y	None	NA	Location at which patient had TP: physician's office/hospital (73%), blood bank (25%), home (0.1%)	Some or all symptoms improved with therapy: 86% Mean time for improvement: 39 (SD, 67) wk New symptoms developed despite treatment: 33% **Sign/Symptom** — **RS, *n* (%)** — **I, *n* %†** — **W, *n* %‡** Fatigue — 1296 (45.5) — 705 (54.4) — 223 (17.2) Joint pain — 1241 (43.5) — 115 (9.2) — 422 (34.0) Impotence/loss of libido — 735 (25.8) — 93 (12.7) — 204 (27.8) Skin bronzing — 733 (25.7) — 431 (58.8) — 30 (4.1) Heart fluttering — 679 (23.8) — 42 (6.2) — 69 (10.1) Depression — 592 (20.8) — 242 (40.8) — 61 (10.3) Abdominal pain — 578 (20.3) — 129 (22.3) — 69 (11.9) Compared with NHANES II and III, similar proportion of patients reported arthritis, liver or gallbladder disease, and extreme fatigue as general population	65% of patients with symptoms said the benefit of treatment outweighed difficulties 20% found the process routine and expressed indifference 12% expressed a negative attitude toward TP that they attributed to poor venous access, time involved, dissatisfaction that the removed blood was discarded	Fair
Powell et al., 2006 (58)	First-degree relatives of C282Y homozygotes with clinical HC or screened population with elevated serum iron measures Australia Prospective cross-sectional study	*n* = 672 401 from family screening; 271 from primary care screening Underwent biopsy after TP: 25 Patients were those with "uncertainty about cirrhosis or persistently abnormal liver enzyme levels" White: predominantly Men: 53%	Homozygotes identified from family or primary care screening Those with high alcohol intake were not analyzed for changes in cirrhosis/fibrosis (*n* = 5)	None	Up to 24 years	TP until TS < 0.15 or SF level ≤ 20 μg/L	NR because of high alcohol intake: 5 of 25 (20%) Improved fibrosis score: 19 of 20 (95%) No change in cirrhosis: 1 of 20 (5%)	NR	Fair

* AD = at diagnosis; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HC = hemochromatosis; I = improved; NA = not available; NHANES = National Health and Nutrition Examination Survey; NR = not reported; Pt = patient; RR = relative risk; RS = reported symptom; SF = serum ferritin; TP = therapeutic phlebotomy; TS = transferrin saturation; U = unchanged; W = worse.
† Improved with therapy.
‡ Worsened despite therapy.

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

Study, Year (Reference)	Setting, Time Frame, Country	Study Design	Sample	Risk Group Definition	Inclusion and Exclusion Criteria	Population	Initial Screening Sequence	Definition of Clinical HC	Diagnostic Criteria	Results	Quality
Family setting											
Barton et al., 1999 (57)	Southern Iron Disorder Center and Brookwood Medical Center No dates reported United States	Cross-sectional study: to compare phenotyping and *HFE* genotyping for diagnosis of hereditary HC in 150 family members of 61 probands	Probands diagnosed during routine 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)	Relatives of people with iron overload (probands: 16% had cirrhosis and 5% had diabetes attributable to iron overload)	Inclusion: willingness of probands and a family member to participate Exclusions: NR	72 (48%) men 78 (52%) women Mean age, 46 (SD, 15) y (All were adults except one 11-year-old) 94 were 1st-degree relatives; 56 were 2nd-degree non–blood relatives	Simultaneous genetic testing for *HFE* alleles C282Y and H63D; phenotype testing using TS; SF measurement	Phenotype definition: elevated fasting TS on ≥ 2 occasions without other known causes (>0.60 [men] and >0.50 [women]) Iron overload: elevated SF level (>300 μg/L [men] and >200 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	HC phenotype: presence of elevated TS or iron overload or both	1st- and 2nd-degree relatives, C282Y/C282Y homozygotes: 25 of 112 (calculated) C282Y/C282Y homozygotes, *n/n (%)*: Siblings: 14/42 (33) Parents: 3/16 (19) Offspring: 5/36 (14) Other blood relatives: 3/18 (16) 22 of 61 probands: blood relative with hereditary HC (36%); all were C282Y/C282Y Phenotype, *n/n (%)*: First-degree relatives: 30/94 (31.9) Non–first-degree relatives: 4/56 (7.1) **C282Y/C282Y, *n*** / **C282Y/H63D, *n*** / **Other, *n*** / **Total, *n/n (%)*** Cirrhosis 2 / 0 / 0 / 2/112 (1.7) Diabetes 4 / 0 / 0 / 4/112 (3.6)	Good/fair
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 169 patients were identified with an index symptom (diabetes, AR, unexplained fatigue, abdominal pain, liver disease, abnormal LFT results, impotency, premature amenorrhea, 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 specialty 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* = 159 Sex: NR Age: 64 (SD, 12) y AR *n* = 62 Sex: NR Age: 61.3 (SD, 13.9) y Diabetes *n* = 121 Women: *n* = 42 Men: *n* = 79 Age: 54.8 (SD, 8.3) y F/A *n* = 227 Women: *n* = 144 Men: *n* = 83 Age: 58.3 (SD, 15.6) y Controls: *n* = 991 (random sample of 2337) Women: *n* = 483	*HFE* C283Y and H63D mutations, serum iron, SF	NA	NA	**Geno†** / **HV (*n* = 991)** / **PC (*n* = 60)** / **OS (*n* = 159)** / **AR (*n* = 62)** / **DM (*n* = 121)** / **F/A (*n* = 227)** HH/CC 60.9 / 68.3 / 56.0 / 59.7 / 42.1‡ / 44.9‡ HD/CC 26.4 / 23.3 / 29.0 / 25.8 / 24.0 / 21.6 HH/CY 6.8 / 5.0 / 10.0 / 8.0 / 14.9§ / 10.6 DD/CC 2.7 / 3.3 / 2.5 / 6.5 / 5.0 / 9.3‡ HD/CY 2.9 / 0 / 1.9 / 0 / 8.3‡ / 7.9§ HH/YY 0.2 / 0 / 0.6 / 0 / 5.8‡ / 5.7‡ **Pheno** / **HV (*n* = 991)** / **PC (*n* = 60)** / **OS + AR (*n* = 221)** / **DM (*n* = 121)** / **F/A (*n* = 227)** TS > 0.40, % Pts w/ TS >0.40 who are YY, *n/n (%)* 2/293 (0.07) / NR / 1/9 (11.1) / 7/106 (6.6) / 13/70 (18.6) SF >300 μg/L, % Pts with SF >300 μg/L who are YY, *n/n (%)* 0/57 (0) / NR / 1/9 (11.1) / 6/56 (10.7) / 13/75 (17.3) TS > 0.40, % 29.6 / NR / 4.1 / 87.6 / 30.8 SF >300 μg/L, % 5.8 / NR / 4.1 / 46.3 / 33.0	Fair

Appendix Table 10—**Continued**

Study, Year (Reference)	Setting, Time Frame, Country	Study Design	Sample	Risk Group Definition	Inclusion and Exclusion Criteria	Population	Initial Screening Sequence	Definition of Clinical HC	Diagnostic Criteria	Results	Quality
			(including those with unstable diabetes) Internal medicine clinics: 227 patients with chronic fatigue and AR Controls: recruited from 2337 persons >18 y from health appraisal center			Men: *n* = 508 Age: 42.5 (SD, 14.9) y OS based on radiographic analysis; AR based on clinical diagnosis Diabetes divided into 3 groups: type 1, type 2, and could not be classified F/A defined by referral to internal medicine for chronic problem					
Deugnier et al., 2002 (51)	Men and women attending Health Appraisal Centres from September 1998 to December 2000 France	Cross-sectional study	Men: age 25–40 y Women: age 35–50 y	Family history of iron excess Chronic fatigue Increased ALT levels	Included: Attending Health Appraisal Centres; meeting age criteria Those who declined genotyping (4%) had no personal history of iron excess	*n* = 9396 (96% of total population) Men: *n* = 3367 Women: *n* = 6029	Questionnaire; age, sex, BMI, awareness of a family relative regularly having TS for iron excess, personal history of blood donation, chronic fatigue, chronic distal AR, diabetes *HFE* C282Y mutation testing, and if C282Y homozygote Fasting serum iron status (iron, TS, and SF) and genetic counseling	*HFE* C282Y mutation testing	NA	C282Y homozygotes by family history of iron excess, *n/n (%)*: Men Family history: 3/83 (3.6) (calculated) No family history: 7/3904 (0.2) (calculated) Women Family history: 12/16 (75) (calculated) No family history: 21/175 (12) (calculated) C282Y homozygotes, *n/n (%)* All participants: 54/9396 (0.006) Men: 10/3367 (0.003) Women: 44/6029 (0.007) C282Y homozygotes by presence of chronic fatigue, *n/n (%)*: Men Chronic fatigue: 7/828 (0.85) (calculated) No chronic fatigue: 3/2180 (0.14) (calculated) Women Chronic fatigue: 12/2253 (0.53) (calculated) No chronic fatigue: 28/3361 (0.83) (calculated) C282Y homozygotes by increased ALT level, *n/n (%)*: Men ALT level increased: 1/176 (0.57) (calculated) ALT level not increased: 9/3181 (0.28) (calculated) Women ALT level increased: 3/322 (0.62) (calculated) ALT level not increased: 42/5694 (0.74) (calculated)	Fair
CHD, CAD											
Waalen et al., 2002 (62)	Health appraisal center in San Diego, California May 1999–August 2001 United States	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	*n* = 35 792 All white, non-Hispanic adult patients age ≥25 y who attended a health appraisal center between May 1999 and August 2001	History of CHD, defined as "yes" to questions "Have you had a heart attack for which you were hospitalized for at least 3 days?" or "Do you have angina pectoris?" or an ICD-9 code of 410 or 412 in the medical record	Inclusion: white, non-Hispanic, age 25–98 y attending Health Appraisal Center of an HMO 46% gave consent for *HFE* mutation testing	Men: *n* = 15 362 Women: *n* = 15 554 All participants were white, non-Hispanic	400-Item questionnaire supplemented with medical record review to ensure ascertainment of all CHD events Serum iron, TS, and SF values *HFE* C282Y and H63D mutations	NA	TS > 0.55 (men) or >0.45 (women), SF level >250 μg/L (men) and >200 μg/L (women) were used to define elevated levels based on clinical criteria	C282Y/C282Y, *n/n (%)*: Men All CHD: 3/1798 (0.17) No CHD: 65/8540 (0.76) Women All CHD: 3/1074 (0.28) No CHD: 65/9117 (0.71)	Good

Continued on following page

Appendix Table 10—**Continued**

Study, Year (Reference)	Setting, Time Frame, Country	Study Design	Sample	Risk Group Definition	Inclusion and Exclusion Criteria	Population	Initial Screening Sequence	Definition of Clinical HC	Diagnostic Criteria	Results	Quality
Liver disease clinics											
Poullis et al., 2003 (63) Moodie et al., 2002 (64)	Patients attending a liver clinic at a teaching district general hospital in south London 1997–2001 London, United Kingdom	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	667 outpatients referred for investigation of liver disease over 5 y 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	Outpatients referred to a liver clinic for investigation of liver disease	Exclusion: previous diagnosis of hereditary HC	n = 667 Age range, 17–83 y (median, 51 y) European: 68.6% (Celtic, 38.4; other, 30.2%); Asian, 10.7%; Afro-Caribbean, 9.7%; Mediterranean, 7.9% Other, 3.1% Previous diagnoses: hepatitis C, 28%; primary biliary cirrhosis, 6%; hepatitis B, 4% Liver biopsy: n = 349 Previous diagnosis: 60% >30 units per week alcohol consumption, present or past history	Nonfasting TS; those with TS >0.45 or a liver biopsy had *HFE* genotyping Indications for biopsy included C282Y homozygosity, C282Y/H63D compound heterozygosity, elevated TS (>0.60), unexplained parenchymal liver disease, persistently abnormal LFT results, and liver disease of known cause necessitating staging or assessment of disease progression	NA	TS cutoffs	11 of 156 (7.1%) patients with TS >0.45 were C282Y/C282Y 1 of 349 (0.03%) patients with liver disease who had liver biopsy were C282Y/C282Y Prevalence of new cases of hereditary HC cases in patients of European origin attending a liver clinic, detected by phenotypic screening over a 5-y period, was 2.8% (12 of 458) (calculated) (Europeans only)	Fair
Arthritis											
Willis et al., 2002 (65)	Specimens of patients with arthritis from the DNA archive of NOAR First diagnosed between 1989 and 1995 United Kingdom	Case–control study: to determine the value of screening patients with inflammatory arthritis for hereditary HC–associated mutations in the *HFE* gene	Case-patients: unselected inflammatory arthritis population collected by NOAR; prevalence of the hereditary HC–associated *HFE* genotypes compared with that in a large sample from unaffected populations Controls: 1000 individuals from the catchment area of the Norfolk and Norwich hospitals, a large subset of the area covered by NOAR	People with inflammatory arthritis	Case-patients: Inclusion: Sequential DNA samples from patients for whom adequate DNA samples remained and who were first diagnosed between 1989 and 1995; >1 swollen joint lasting for > 6 wk Controls: Exclusions: Patients with HC and people with foreign names	Arthritis populations: n = 1000 Controls: 373 unaffected volunteers from screening trial and 541 patients undergoing full blood counts Mean age, 54 y	*HFE* C282Y and H63D mutation testing	NA	NA	**Variable** Mean age, *y* C282Y homozygotes, *n* Predicted frequency of C282Y homozygotes (95% CI)	**Arthritic Patients** 54 5 1 in 287 (190–403)	**Controls** 54 5 1 in 236 (170–335)	Good

Appendix Table 10—**Continued**

Study, Year (Reference)	Setting, Time Frame, Country	Study Design	Sample	Risk Group Definition	Inclusion and Exclusion Criteria	Population	Initial Screening Sequence	Definition of Clinical HC	Diagnostic Criteria	Results	Quality
CFS											
Swinkels et al., 2002 (66)	Department of General Internal Medicine of the University Medical Centre St. Radbound, Nijmegen, a Dutch tertiary CFS referral center 1992 The Netherlands	Cross-sectional study: to determine whether patients previously diagnosed as having CFS actually have primary HC	NR	Patients fulfilling criteria for CFS Patients had given permission to store serum for future CFS studies	NR	88 self-referred patients previously diagnosed with CFS Mean age, 40 y (range, 20–66 y) Men: $n = 23$ Women: $n = 65$	TS: elevated if >0.40 (women) and >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 μg/L [men], 6–80 μg/L [premenopausal women], and 15–190 μg/L [postmenopausal women]) Elevated TS: $n = 6$ Elevated SF level: $n = 2$ Elevated TS and SF level: $n = 0$	NA	NR	None of the 8 patients with increased TS or increased SF levels were C282Y homozygotes or compound C282Y/H63D heterozygotes	Fair/ poor

* 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.
‡ $P \leq 0.001$; 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.

Appendix Table 11. **Study Pending Assessment for Key Question 1**

Study Citation	Comment
Falize L, Guillygomarch A, Perrin M, Laine F, Guyader D, Brissot P, et al. Reversibility of hepatic fibrosis in treated genetic haemochromatosis: a study of 28 cases [Abstract]. Bioiron Proceedings, May 2005; P234.	Abstract from a meeting. No article published yet.