

Hereditary hemochromatosis: Perspectives of public health, medical genetics, and primary care

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Hereditary hemochromatosis (HHC) is a condition characterized by excess iron in body tissues, resulting in complications such as cirrhosis, cardiomyopathy, diabetes, and arthritis. These complications usually manifest during adulthood. Two methods of screening for the detection of early stage of HHC are available: serum iron measures and molecular testing to detect mutations in the *HFE* gene. These phenotypic and genotypic screening tests are of particular interest because a simple treatment—periodic phlebotomy—can be used to prevent iron accumulation and clinical complications. HHC might represent the first adult-onset genetic disorder for which universal population-based screening would be appropriate. Therefore, HHC has been proposed as a paradigm for the introduction of adult genetic diseases into clinical and public health practice. However, universal screening for HHC has not been recommended because of the uncertainty about the natural history of the iron overload or HHC and, in particular, uncertainty about the prevalence of asymptomatic iron overload and the likelihood that it will progress to clinical complications. If universal screening is not appropriate based on current data, what other measures might reduce the disease burden of iron overload? New studies provide more systematic information about the penetrance of the *HFE* C282Y mutation and shed further light on the natural history of the disorder. The authors review these data and consider their implications for public health, medical genetics, and primary care.

Genet Med 2003;5(1):1–8.

Key Words: hereditary hemochromatosis, screening, genetics, *HFE*, gene, iron overload

Hereditary hemochromatosis (HHC) has been proposed as a paradigm for the introduction of adult genetic diseases into clinical and public health practice. This disorder, inherited as an autosomal recessive condition, can result in the accumulation of iron in body tissues, resulting in complications such as cirrhosis, cardiomyopathy, diabetes, and arthritis.¹ Two methods of screening for early detection of the disease are available: serum iron measures and molecular testing to detect mutations in the *HFE* gene.² These phenotypic and genotypic screening tests are of particular interest because a simple treatment—periodic phlebotomy—can be used to prevent iron accumulation and clinical complications. These characteristics suggest that HHC might represent the first adult-onset genetic disorder for which universal population-based screening would be appropriate.

When policy-makers began to consider this screening option, however, important knowledge gaps were identified.^{2–5} Little was known about the natural history of iron overload or HHC and, in particular, about the prevalence of asymptomatic iron overload or the likelihood that it would progress to clinical complications. No population-based data were available to address these questions. Studies of patients seen in referral centers provided only partial insight into the natural history of HHC. Some studies suggested that iron accumulation occurred progressively over time, but that the rate was highly variable. Yet the answer to the most important question, the proportion of people with a mild degree of iron overload who would progress to clinically apparent disease, remained uncertain.

The discovery of the *HFE* gene provided a new tool to evaluate these questions.⁶ Multiple studies in clinical centers confirmed that the majority of people with a diagnosis of HHC are homozygous for the C282Y mutation of the *HFE* gene.⁷ A second *HFE* mutation, H63D, contributes to risk for iron overload as well, when in the homozygous state or as a compound heterozygotes with C282Y.⁸ However, genotyping also raised questions about the natural history of the disease. Families were described wherein some siblings with C282Y homozygosity had classical symptoms of HHC while other siblings with the same genotype remained asymptomatic into old age.^{1,2}

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Received: August 30, 2002.

Accepted: November 5, 2002.

DOI: 10.1097/01.GIM.0000047946.94270.34

On the basis of these data, many policy-makers concluded that additional information was needed before universal screening for HHC could be considered.^{2–5} If universal screening is not appropriate based on current data, what other measures might reduce the disease burden of iron overload? New studies provide more systematic information about the penetrance of the *HFE C282Y* mutation and shed further light on the natural history of the disorder. In this article we review these data and consider their implications for public health, medical genetics, and primary care.

NATURAL HISTORY OF HHC

Insights from prevalence studies using serum iron measures

The prevalence of HHC and iron overload can be estimated by using serum iron measures. Most studies have used transferrin saturation (TS = serum iron/total iron binding capacity \times 100) and serum ferritin to identify individuals at risk,^{1,9} followed by liver biopsy or quantitative phlebotomy to determine those who are iron-overloaded. However, data comparisons are complicated by differences in screening protocols (e.g., selection of initial screening test, screening thresholds for TS and serum ferritin), populations selected for study, and definitions of iron overload. Most studies have been done in populations of predominantly European descent. Taken together, these studies provide a rough estimate of the prevalence of iron overload in this population.

Iron overload has also been observed in African Americans and in African populations, but it is not well characterized

clinically; estimates of prevalence in this population are not available.^{10–12} Some observations indicate that the predominant mechanism of iron overload is different: TS levels may be lower in people of African descent with iron overload, with iron accumulating primarily in Kupffer cells,¹³ as compared to hepatocytes in HHC. As with HHC, family studies suggest a causative genetic factor.

Elevated TS represents the earliest phenotypic finding in HHC. Recommendations for the threshold definition of elevated TS have ranged from 45% to 62%.¹⁴ In the US adult population, the prevalence of elevated TS on random blood draw ranges between 1% and 6%, depending on the value used to define an elevated level.¹⁴ Among persons with an initial elevated TS, repeated testing (usually done on a fasting specimen) has revealed a persistently elevated level in 15% to 54% of persons (Table 1).^{15–22} On the basis of these data, the estimated population prevalence of persistently elevated TS varies from 0.3% to 2.0% (Table 1).^{15–22} These studies also reported that elevated serum ferritin levels were found in 0% to 61% of those with persistently elevated TS.^{15,16,19,21} Confirmatory testing provided evidence of iron overload in about half of subjects with persistently elevated TS^{17,20} and in 60% to 100% of subjects with elevations in both TS and serum ferritin.^{16,23} The wide range of estimates reported in these studies reflects differences in study characteristics noted previously; however, all observe a drop-off in subjects with positive test results with each step in the testing pathway (Table 1).²⁴

Table 1
Screening with transferrin saturation: Comparison of initial and revised screen positive rates in published screening trials

Study	Initial % TS cutoff level	Initial positive rate (%)	Repeat TS cutoff level	Revised positive rate (%)	Persons with initial elevated TS who had second positive test (%)
Lindmark and Eriksson, 1985 ¹⁵	≥ 60	20/941 (2.1)	≥ 60	6/941	30
Edwards et al., 1988 ¹⁶	≥ 62	221/11,065 (2.0)	≥ 62 Fasting	35/11,065 (0.3)	16
Edwards et al., 1988 ¹⁶	≥ 50	688/11,065 (6.2)	≥ 50 Fasting	103/11,065 (0.9)	15
Leggett et al., 1990 ¹⁷	> 45	46/1,968 (2.3)	> 45	18/1,968 (0.9)	39
Baer et al., 1995 ²²	≥ 62	40/3,977 (1.0)	≥ 62 Fasting	14/3,977 (0.4)	39
Smith et al., 1997 ¹⁸	≥ 55	24/2,294 (1.1)	≥ 55 Fasting	13/2,294 (0.6)	54
Phatak et al., 1998 ¹⁹	≥ 45	932/16,031 (5.8)	≥ 45 Fasting	311/15,846 (2.0)	42
Burt et al., 1998 ²⁰	> 55	39/1,064 (3.7)	55 Fasting	13/1,064 (1.2)	33
McDonnell et al., 1999 ²¹	≥ 50 F ≥ 60 M	60/1,653 (3.6)	≥ 50 F ≥ 60 M Fasting	13/1,653 (0.8)	22

Few studies, however, have assessed the proportion of persons with iron overload who have clinical disease. Bradley et al.²⁵ evaluated this question in a review of population-based studies. The studies were included if they confirmed iron overload by liver biopsy or quantitative phlebotomy and collected information on clinical complications, including liver fibrosis, liver cirrhosis, cardiomyopathy, arthropathy, diabetes, abdominal pain, and hepatomegaly. At the time these studies were conducted, *HFE* genotyping was not available. In the pooled analysis, 54% of subjects with iron overload (58% of men and 44% of women) had one or more of these complications. For some, the only finding was asymptomatic liver fibrosis; clinical symptoms were reported in 27% of men (half of those with clinical findings) and 33% of women (75% of those with clinical findings). However, these studies of symptomatic patients did not use control groups; as a result, it is difficult to estimate the proportion of clinical findings attributable to iron overload. This proportion could be very low: for example, studies of patients with end-stage complications of HHC have consistently found fewer affected women than men,^{1,26,27} suggesting that at least some clinical findings among women identified in prevalence studies are due to other causes. Similarly, a population-based study using TS level as the primary screening method found fewer women than men with significant morbidity.²⁸

Bradley et al.²⁵ calculated the weighted average for prevalence of iron overload to be 0.25%; correcting for missed diagnoses and compliance, the authors estimated actual prevalence of iron overload to be 0.5% in men and 0.6% in women.²⁵ Other studies suggest a prevalence of iron overload ranging from 0.06% to 0.4%.²⁴ Assuming that one third to one half of people with iron overload have clinical symptoms, these figures suggest that the prevalence of clinical disease due to iron overload is in the range of 0.02% to 0.25%. By comparison, autopsy studies have reported pathological evidence of iron overload in the liver in 0.09% to 0.19% of specimens.^{15,29,30} The prevalence of recognized HHC as a cause of death is lower, ranging between 0.017% and 0.032%.³¹

Estimates for the prevalence of iron overload and associated clinical symptoms based on serum iron measures vary over a 10-fold range. At the upper end (0.4–0.5%), the estimates are in the same range as the prevalence of the C282Y/C282Y genotype.

Insights from prevalence studies using *HFE* genotype

Many studies have evaluated the prevalence of the two *HFE* mutations associated with iron overload, C282Y and H63D, in different populations around the world. These studies (reviewed by Hanson et al.⁷) document that the C282Y mutation and C282Y homozygosity are most prevalent in populations of European descent. Because the C282Y homozygous genotype accounts for the majority of clinically diagnosed cases of HHC, these data support congruence between iron overload in people of European descent and HHC. This overlap is likely to be most complete in populations of Northern European descent.

Other rare genetic causes of iron overload have been described in European populations. In Southern Europe, families with a clinical entity indistinguishable from HHC have been described, but genetic studies document causative mutations in two other genes, *TFR2* and *SLC11A3*.^{32–38} Another rare disorder, juvenile hemochromatosis, is inherited as an autosomal recessive disorder linked to chromosome 1 and results in severe iron overload by the second decade of life; males and females are equally affected.^{36,39} These genetic entities appear to account for only a small proportion of persons with iron overload.

A pooled analysis of population studies of *HFE* genotypes found a prevalence of 0.4% (95% confidence interval [CI] 0.3–0.5%) for the C282Y/C282Y genotype, 1.6% (95% CI 1.4–1.9%) for the C282Y/H63D genotype, and 1.9% (95% CI 1.6–2.1%) for the H63D/H63D genotype.⁷ Similarly, the three largest population-based genotype frequency studies in the United States estimated a prevalence for C282Y homozygosity of 0.3% (95% CI 0.1–0.5), 0.4% (95% CI 0.2–0.9), and 0.5% (95% CI 0.3–0.6) (Table 2).^{21,40,41} These data are relatively consistent; observed differences are likely be due to differences in racial/ethnic distributions in the populations studied.

The pooled analysis of *HFE* genotypes found that 77.5% (95% CI 75.9–78%) of HHC cases have the C282Y/C282Y genotype.⁷ A range of other *HFE* genotypes including C282Y/H63D (5.3%, 95% CI 4.5–6.2%) and H63D/H63D (1.5%, 95% CI 1.1–2.1%) is found in the remaining cases; some cases carry either a single *HFE* mutation or none at all.⁷

Penetrance of the C282Y/C282Y genotype

Calculation of *HFE* genotype penetrance—that is, the proportion of persons with the genotype who have (or will develop) clinical disease—represents another way to estimate the prevalence of clinical complications of HHC. Four studies have estimated the penetrance of C282Y homozygosity, the *HFE* genotype conferring the highest risk. In a Utah study, unselected relatives of HHC patients were tested for iron status and clinical symptoms.⁴² Among 214 relatives, *HFE* mutation testing was done in 158; 87% of these had the C282Y/C282Y genotype. The study used a low threshold for iron overload: serum ferritin >325 $\mu\text{g/L}$ in males or 125 $\mu\text{g/L}$ in females, or a liver biopsy revealing at least 25 μmol of iron/g dry weight (for a man aged 50 years, this level of liver iron would result in a hepatic index of 0.5, compared with the usual threshold of 1.9 cited for diagnosis of HHC).⁴³ By these criteria, most relatives had iron overload. However, evidence of liver disease was relatively infrequent: Among all male subjects, 12% had cirrhosis (95% CI 7–20%) and 12% had liver fibrosis (95% CI 6–19%), while for females the comparable figures were 2% (95% CI 0.2–7%) and 4% (95% CI 1–10%). A small proportion of patients also had HHC-related arthropathy as detected by radiologic examination. More than 90% of these subjects reported nonspecific symptoms that could be caused by iron overload, including arthralgia, weakness, and abdom-

Table 2
HFE genotype frequencies in the general population

Study population	Genotype						Subjects	References
	C282Y/+ frequency (%) (95% CI)	C282Y/C282Y frequency (%) (95% CI)	H63D/+ frequency (%) (95% CI)	H63D/H63D frequency (%) (95% CI)	C282Y/H63D frequency (%) (95% CI)	+/+ frequency (%) (95% CI)		
NHANES III	8.3 (7.5–9.3)	0.3 (0.1–0.5)	21.4 (20.0–22.8)	1.9 (1.5–2.4)	2.0 (1.5–2.5)	66.2 (64.6–67.7)	N = 5171; population-based samples in the DNA bank from the US Third National Health and Nutrition Examination Survey	Steinberg et al., 2001 ⁴⁰
United States (California)	8.5 (7.9–9.0)	0.5 (0.3–0.6)	22.2 (21.3–23.0)	2.2 (1.9–2.5)	1.7 (1.5–2.0)	66.0 (64.0–66.0)	N = 9390; adults attending health appraisal clinic of health maintenance organization	Beutler et al., 2000 ⁴¹
United States (Missouri)	8.9 (7.5–10.5)	0.4 (0.2–0.9)	23.9 (21.8–26.2)	3.4 (2.6–4.5)	2.5 (1.7–3.3)	60.9 (58.3–63.4)	N = 1450; health maintenance organization employee volunteers	McDonnell et al., 1999 ²¹

inal pain, but no comparison group was evaluated. As a result, the proportion of these symptoms attributable to HHC could not be determined.

Similarly, a population-based study in Australia ($N = 3,011$)²⁸ identified 16 C282Y homozygotes (for a population prevalence of 0.5%), of which 8 had clinical findings: hepatomegaly in 3 [43% (3 of 7) (95% CI 10–82%)] of males and none (0 of 9) of females (95% CI 0–34%) and skin pigmentation and/or arthritis in the other 5. No comparison group was included.

A screening study at a health maintenance organization in southern California provided additional information about the clinical status of persons homozygous for C282Y.⁴⁴ TS was $\geq 50\%$ in 75% of males and 40% of females and serum ferritin was $\geq 250 \mu\text{g/L}$ in 76% of men and $>200 \mu\text{g/L}$ in 54% of females. Compared with control subjects, persons homozygous for C282Y were more likely to have a history of “liver and hepatitis problems” (8% vs. 4%), elevated serum aspartate aminotransferase (8% vs. 4%), and elevated plasma collagen IV, a measure associated with hepatic fibrosis (26% vs. 11%). However, C282Y homozygotes were no more likely to have a history of fatigue, joint pain, impotence, skin pigmentation, or diabetes. Among all 152 subjects with the C282Y/C282Y genotype, only 1, an alcoholic, had a clinical history of end-stage HHC. Two of 119 with complete data had markedly abnormal laboratory values suggestive of severe liver fibrosis. The authors estimated the penetrance of significant clinical disease in persons with the C282Y/C282Y genotype at about 1%.

In addition, the California study found a similar prevalence for the C282Y/C282Y genotype among older and younger subjects.⁴⁴ A United Kingdom study obtained a similar result: the prevalence of the C282Y/C282Y genotype was 0.67% among elderly men, suggesting no loss of this genotype in men at older ages.⁴⁵ These observations also argue for low penetrance of the

C282Y/C282Y genotype, because clinical complications resulting in early mortality would be expected to reduce the prevalence of the genotype at older ages.

A fourth study assessed clinical disease in a population-based sample of 65,238 adults above age 20 in Norway (median age 49).⁴⁶ HHC was diagnosed on the basis of persistently elevated TS, elevated serum ferritin, and the absence of other medical explanations for these abnormalities. Among 92 women and 177 men with HHC diagnosed as a result of the screening study, 85% had the C282Y/C282Y genotype. A third of persons with HHC had elevated serum transaminase levels, and 4% had diabetes. Fatigue was reported by 16% of women and 14% of men, joint pain by 13% of women and 20% of men; 3% of men reported impotence. No comparison group was evaluated. In addition, no clinical information was reported on three women and six men with HHC diagnosed prior to the screening study.

These studies have important limitations. The Utah, Australian, and Norwegian studies failed to include comparison groups. In addition, the Utah study evaluated relatives of patients with clinical disease due to HHC, a group that might be more likely to develop clinical disease due to shared environment or genetic background. Conversely, the California study drew subjects from a prevention clinic, thus potentially selecting against patients with clinical disease. In addition, this study could not fully evaluate 28 of the 152 C282Y homozygotes; the authors state that these subjects, for whom questionnaire data were not available, were diagnosed on the basis of screening. Despite the potential biases, these studies all suggest that only a minority of C282Y homozygotes develop clinical disease attributable to iron overload. However, the actual proportion with clinical symptoms remains uncertain. Considering these studies and those based only on iron measures, the clinical penetrance of HHC could range from 1% to 50%.

IMPLICATIONS OF PREVALENCE AND PENETRANCE DATA

Population screening

Although population screening is a logical consideration for HHC, given the prevention opportunity provided by phlebotomy, it now seems likely that a significant proportion of people with *HFE* mutations or mild iron overload will *not* develop clinical complications of HHC. Screening would generate many false-positive findings, resulting in unnecessary treatment and the potential for stigma or discrimination associated with a diagnosis of hemochromatosis.

However, low penetrance would not necessarily rule out a population screening approach if a benefit could be proven. For example, screening for elevated blood pressure and hyperlipidemia is routinely recommended, even though only a minority of persons with elevated levels benefit from treatment.⁴⁷ Although we cannot predict which individuals will develop the clinical complications of these conditions, routine treatment results in reduced cardiovascular disease overall. By analogy, identification and treatment of all persons with biochemical evidence of iron overload might be merited, to prevent clinical complications in some. As with treatment of hypertension and hyperlipidemia, this recommendation can be made only if controlled studies document a health benefit in screened compared with unscreened populations. Data about the social implications of screening would also be relevant. For example, current blood safety policies in the United States bar persons with hemochromatosis from routine blood donation, so that phlebotomy must be pursued as a relatively costly medical procedure. Data supporting a change in blood safety policy could potentially reduce the burden for persons who test positive in a screening program. Without additional data, population screening is difficult to justify. As a result, further studies of the potential benefits and risks of screening represent an important research priority.

Medical genetics practice

Family-based detection represents an important alternative approach to identifying people with iron overload. When a diagnosis of HHC is made, it also identifies family members who represent a group with a markedly higher a priori risk of

iron overload disease than the general population. Therefore, it is reasonable to consider assessment of iron status in relatives and to monitor them for symptoms suggestive of iron overload.

HFE genotyping provides a one-time test to determine which relatives of an identified proband have an increased risk of iron overload. These relatives can be offered ongoing surveillance, while others can be reassured. However, genotyping may also cause confusion about clinical status and adverse labeling, so the value of genotyping as a method for family-based detection of HHC is not entirely clear. Issues to be considered are summarized in Table 3.

Siblings of an affected person with the homozygous C282Y genotype have a 25% chance of sharing the same high-risk genotype; for siblings who do not share the genotype, this single test can greatly reduce the risk. However, HHC has occurred in some people with other *HFE* genotypes (e.g., C282Y/H63D, C282Y/+),⁷ suggesting the need for caution in the interpretation of a “negative” test result. But even the implications of a “positive” result are not straightforward; current penetrance data make risk of disease hard to calculate even for relatives with a C282Y/C282Y genotype and argue against making a diagnosis of HHC on the basis of genotype alone.² In the uncommon instance of a proband with a different *HFE* genotype, genotypic studies of relatives are even more difficult to assess, given the very low penetrance of genotypes other than C282Y/C282Y.⁸

Testing of offspring raises even more questions, because of the high carrier rate for *HFE* mutations (e.g., 9% for C282Y, 23% for H63D in populations of European descent⁷). If the parent with HHC is a C282Y homozygote, offspring have a 4.5% likelihood of inheriting the same genotype (calculated as follows: 100% chance of inheriting the C282Y allele from the affected parent × 9% chance that the other parent is a C282Y carrier × 50% chance of inheriting C282Y from the unaffected parent) and an 11.5% chance of inheriting a C282Y/H63D genotype. All other offspring will be C282Y carriers. Because disease occurs in middle age, there is no rationale for testing during childhood.⁴⁸

Many genotypic results thus have some ambiguity. Although risk of iron overload is low for all genotypes other than

Table 3
Genotype testing in relatives of patients with HHC

Proband genotype	Potential benefits	Potential risks
C282Y/C282Y	Provide ongoing monitoring of relatives with C282Y/C282Y <i>Sibs</i> : Identify 25% with same genotype; reassure remaining 75% about their low risk <i>Offspring</i> : Identify 4.5% with same genotype; reassure remaining 95.5% about their low risk	Adverse effects of genetic labeling: Discrimination based on positive genetic test in asymptomatic person Misunderstanding of negative results, especially for C282Y carriers, and for 11.5% of offspring with C282Y/H63D genotype
C282Y/H63D H63D/H63D	Provide ongoing monitoring of relatives with same <i>HFE</i> genotype as proband	Misunderstanding of both positive and negative test results

C282Y/C282Y, there is evidence that genetic test results may be misinterpreted. For example, both false reassurance and the assumption that the carrier state confers health risks have been reported after cystic fibrosis carrier testing.^{49,50} And a generally reassuring study of the psychosocial impact of *HFE* testing in Canada nevertheless reported that 70% experienced worry after receiving their test result.⁵¹

Genotype testing does not substitute for the serum iron studies needed to identify iron overload, and it could expose the family member to a premature diagnosis, unnecessary treatment, and the potential for stigma and discrimination. These considerations underscore the need for more information about the clinical penetrance of *HFE* genotypes in HHC and about effective ways to counsel patients after genetic testing to ensure an accurate understanding of the results.

Primary care practice

Heightening health care providers' awareness of HHC has been identified as a public health goal.²⁴ Missed diagnoses of HHC provide the rationale for this educational goal. For example, clinical studies have documented previously unsuspected cases of HHC among liver transplant patients and diabetics.^{52,53} In addition, most persons who ultimately receive a diagnosis of HHC have visited doctors for HHC-related symptoms over several years before the diagnosis is made.²¹ Education would have the goal of increasing providers' awareness of HHC as a familial disorder and as a potential explanation for a group of common symptoms (e.g., unexplained fatigue, joint pain, palpitations, abdominal pain, abnormal liver function tests, hepatomegaly, or elevated serum ferritin).

However, deciding when to test for HHC is a difficult problem in primary care practice, given current data indicating a low positive predictive value for testing. In particular, the implications of a positive test for treatment are unclear. Therapeutic phlebotomy is assumed to be effective, based on limited data, and is relatively benign as an isolated procedure. However, complying with this therapy may represent an arduous task over a lifetime and may not provide a compensatory health benefit.

Testing all patients who have the common nonspecific symptoms of HHC would yield few diagnoses.⁵⁴ Fatigue, for example, is found in 10% to 20% of the primary care population and has causes—such as depression, sleep disturbance, and anemia—that are more prevalent than HHC by at least an order of magnitude. Joint pain and abdominal pain are similarly common and multicausal. At what point in the workup of such symptoms should HHC be considered?

A related unresolved question concerns counseling: When should the possibility of a genetic diagnosis be discussed? If a patient presents with fatigue, should counseling about the potential genetic diagnosis be provided before obtaining the first TS? And, before confirming an elevated level? Because many people have nonspecific symptoms that might suggest HHC, and elevated TS occurs in as many as 6% of the population,¹⁴ the opportunity costs of pursuing a diagnosis of HHC could be considerable, particularly in context of data suggesting the low

likelihood of serious complications among those with elevated iron levels.

Some diagnoses, such as diabetes, also represent potential indicators of HHC. Should all newly diagnosed diabetics be tested? Screening for HHC in diabetics (or in patients with other diagnoses or symptoms suggestive of HHC) could lead to early intervention (phlebotomy) on the assumption that it will provide health benefit. But data on this point are insufficient. Diabetes is a “late” complication of HHC; it usually appears when iron overload has already damaged, probably irreversibly, vital organs such as the pancreas.²⁶ For example, a case report of the diagnosis of HHC in a diabetic patient documents a detrimental effect on quality of life, without clear health benefit.⁵⁵ Without controlled studies it is difficult to know whether treatment at this stage is beneficial. The intervention may be assumed to prevent other morbidities associated with iron overload (such as cirrhosis or cardiomyopathy), but these might not, in fact, have occurred. Worse, the lack of other complications following treatment could reinforce its use and preclude objective assessment in a controlled trial.⁵⁶

The question of family-based screening raises interesting challenges for the primary care provider. While testing in relatives of a proband with HHC increases the likelihood of testing positive, the person identified by either genotype or serum iron measures faces the same uncertainty about the benefits of this finding as others identified by screening. As such, the provider would want to engage in an informed/shared decision-making process, to review the benefits and harms of the risk assessment process. Conveying the potential for harm is often a difficult and time-consuming task. Thus policy-makers must consider the implications for primary care practice, including the opportunity costs of the time invested in this encounter.

These observations argue forcefully for more research on the outcomes of testing and treatment in people with suspected early iron overload and in family members after an HHC diagnosis is made. The evidence that would support pursuing the diagnosis of hemochromatosis in patients with either nonspecific symptoms or a disease associated with HHC, such as diabetes, includes the following:

1. The incidence of hemochromatosis is greater in the clinically defined group than in the general population; with the above caveats, this reasoning would support testing for HHC in relatives of affected patients, but screening studies among diabetics in clinical settings to date have been inconsistent^{52,57–62} and the prevalence of HHC among patients with nonspecific symptoms appears low.⁵⁴
2. The predictive value for clinical disease is sufficiently high to warrant testing—however, the predictive value is currently unknown and may be low.
3. Early detection and treatment of hemochromatosis positively affects the health outcome of the patient. No controlled studies have assessed this point. Uncontrolled studies that suggested benefit from phlebotomy²⁶ might

reflect a benign natural history for many patients, independent of treatment.

- Potential benefits of screening, diagnosing, and treating HHC in patients with specific clinical presentations outweigh the adverse effects and costs. While phlebotomy is simple, safe, and most likely an effective preventive treatment for people at risk for the complications of iron overload, the treatment of asymptomatic people with phlebotomy is not without adverse effects, including the burdens and potential complications of liver biopsy (if done) and the potential risk of unjustified discrimination following a diagnosis of HHC.

CONCLUSIONS

Previous calls for HHC screening have been based on the assumption that a high proportion of individuals with positive results of phenotypic or genotypic screening will develop clinical symptoms over time. Current data argue against this assumption, but further research is needed. Most importantly, further investigation of the various factors contributing to clinical complications of iron overload is needed. Research in animal models has identified several genes related to iron metabolism,^{38,63} and variants in these genes might contribute to clinical manifestations of iron overload, either independently or by modifying the effect of an *HFE* genotype. However, recent research has so far failed to find any interaction of such genes.⁶⁴ Nongenetic factors may prove to play a key role in iron overload disease; excess alcohol intake, for example, is a risk factor for cirrhosis among persons with HHC.² This effort should also include investigation of genetic and other contributors to iron overload in non-European populations. Further research is also needed to assess, in a controlled fashion, the health benefits of phlebotomy in people with asymptomatic iron overload or mild, nonspecific symptoms. It could be argued that failure to provide phlebotomy to persons with diagnosed iron overload is unethical, given the potential complications of iron overload and the likely benefit of phlebotomy. However, studies could be designed in an ethical manner to address treatment questions about which there is great uncertainty, such as the level of serum ferritin at which to initiate phlebotomy; or to compare the outcome in a screened versus and unscreened populations.

While awaiting further evidence, clinicians must also respond to the available evidence that iron overload can progress to life-threatening complications in at least some affected individuals. This reality suggests the need for clinical effort in two areas, while the results of further research are awaited:

Health provider education

Primary care providers and other clinicians—including gastroenterologists, hematologists, rheumatologists, cardiologists, and endocrinologists—need to have an appropriate understanding of HHC as a rare but treatable cause of a variety of clinical signs and symptoms. Educational strategies are likely to be most useful if they present HHC as one of several poten-

tial causes of common symptoms with the focus on appropriate workup of the symptom rather than on HHC. Thus guidelines for workup of fatigue might include HHC as a consideration, recognizing that it would not generally be included in the initial workup but would become an increasingly important aspect of the differential diagnosis for symptoms that remained unexplained. Inclusion of HHC in medical school curricula, using the same framework, will also help to increase provider awareness of this diagnosis.

Family-based detection of iron overload

When a diagnosis of HHC is made, clinicians should encourage assessment of family members for evidence of iron overload. The role of genotype in this process requires further assessment. A dialogue between medical genetics and other clinical disciplines may be the best approach to developing clinical practice guidelines for the evaluation of family members. These should take into account uncertainty about the clinical utility of genotypic testing and the importance of avoiding a premature diagnosis of HHC. It is also crucial to involve health care payers in the dialogue, to ensure their support of practice guidelines regarding screening for HHC as they are developed.

References

- Bacon BR, Sadiq SA. Hereditary hemochromatosis: presentation and diagnosis in the 1990s. *Am J Gastroenterol* 1997;92:784–789.
- Adams P, Brissot P, Powell LW. EASL International Consensus Conference on Haemochromatosis. *J Hepatol* 2000;33:485–504.
- Burke W, Thomson E, Khoury MJ, McDonnell SM, Press N, Adams PC et al. Hereditary hemochromatosis: gene discovery and its implications for population-based screening. *JAMA* 1998;280:172–178.
- Haddow JE, Bradley LA. Hereditary haemochromatosis: to screen or not. Conditions for screening are not yet fulfilled. *BMJ* 1999;319:531–532.
- Cogswell ME, McDonnell SM, Khoury MJ, Franks AL, Burke W, Brittenham G. Iron overload, public health, and genetics: evaluating the evidence for hemochromatosis screening. *Ann Intern Med* 1998;129:971–979.
- Feder JN, Gnirke A, Thomas W, Tsuchihashi Z, Ruddy DA, Basava A et al. A novel MHC class I-like gene is mutated in patients with hereditary haemochromatosis. *Nat Genet* 1996;13:399–408.
- Hanson EH, Imperatore G, Burke W. *HFE* gene and hereditary hemochromatosis: a HuGE review. *Human Genome Epidemiology. Am J Epidemiol* 2001;154:193–206.
- Burke W, Imperatore G, McDonnell SM, Baron RC, Khoury MJ. Contribution of different *HFE* genotypes to iron overload disease: a pooled analysis. *Genet Med* 2000;2:271–277.
- Witte DL, Crosby WH, Edwards CQ, Fairbanks VF, Mitros FA. Hereditary hemochromatosis. *Clin Chim Acta* 1996;245:139–200.
- Gordeuk V, Mukiibi J, Hasstedt SJ, Samowitz W, Edwards CQ, West G et al. Iron overload in Africa: interaction between a gene and dietary iron content. *N Engl J Med* 1992;326:95–100.
- Bloom PD, Burstien GR, Gordeuk VR. Iron overload in African Americans. In: Barton JC, Edwards CQ, editors. *Hemochromatosis*. New York: Cambridge University Press, 2000:475–484.
- Barton JC, Edwards CQ, Bertoli LF, Shroyer TW, Hudson SL. Iron overload in African Americans. *Am J Med* 1995;99:616–623.
- Gangaidzo IT, Moyo VM, Saungweme T, Khumalo H, Charakupa RM, Gomo ZA et al. Iron overload in urban Africans in the 1990s. *Gut* 1999;45:278–283.
- Looker AC, Johnson CL. Prevalence of elevated serum transferrin saturation in adults in the United States. *Ann Intern Med* 1998;129:940–945.
- Lindmark B, Eriksson S. Regional differences in the idiopathic hemochromatosis gene frequency in Sweden. *Acta Med Scand* 1985;218:299–304.
- Edwards CQ, Griffen LM, Goldgar D, Drummond C, Kolnick MH, Kushner JP. Prevalence of hemochromatosis among 11,065 presumably healthy blood donors. *N Engl J Med* 1988;318:1355–1362.
- Leggett BA, Halliday JW, Brown NN, Bryant S, Powell LW. Prevalence of hemochromatosis amongst asymptomatic Australians. *Br J Haematol* 1990;74:525–530.

18. 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;25:1439–1446.
19. Phatak PD, Sham RL, Raubertas RF, Dunnigan K, O'Leary MT, Braggins C et al. Prevalence of hereditary hemochromatosis in 16,031 primary care patients. *Ann Intern Med* 1998;129:954–961.
20. Burt MJ, George PM, Upton JD, Collett JA, Frampton CM, Chapman TM et al. The significance of haemochromatosis gene mutations in the general population: implications for screening. *Gut* 1998;43:830–836.
21. McDonnell SM, Hover A, Gloe D, Ou CY, Cogswell ME, Grummer-Strawn L. Population-based screening for hemochromatosis using phenotypic and DNA testing among employees of health maintenance organizations in Springfield, Missouri. *Am J Med* 1999;107:30–37.
22. 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;98:464–468.
23. McDonnell SM, Preston BL, Jewell SA, Barton JC, Edwards CQ, Adams PC et al. A survey of 2,851 patients with hemochromatosis: symptoms and response to treatment. *Am J Med* 1999;106:619–624.
24. Burke W, Reyes M, Imperatore G. Hereditary hemochromatosis: a realistic approach to prevention of iron overload disease in the population. *Best Pract Res Clin Haematol* 2002;15:315–328.
25. Bradley LA, Haddow JE, Palomaki GE. Population screening for haemochromatosis: a unifying analysis of published intervention trials. *J Med Screen* 1996;3:178–184.
26. Niederau C, Fischer R, Pürschel A, Stremmel W, Häussinger D, Strohmeyer G. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology* 1996;110:1107–1119.
27. Moirand R, Adams PC, Bicheler V, Brissot P, Deugnier Y. Clinical features of genetic hemochromatosis in women compared with men. *Ann Intern Med* 1997;127:105–110.
28. Olynyk JK, Cullen DJ, Aquilia S, Rossi E, Summerville L, Powell LW. A population-based study of the clinical expression of the hemochromatosis gene. *N Engl J Med* 1999;341:718–724.
29. MacSween RN, Scott AR. Hepatic cirrhosis: a clinico-pathological review of 520 cases. *J Clin Pathol* 1973;26:936–942.
30. MacDonald R. Hemochromatosis and cirrhosis in different geographic areas. *Am J Med Sci* 1965;249:36–46.
31. Yang Q, McDonnell SM, Khoury MJ, Cono J, Parrish RG. Hemochromatosis-associated mortality in the United States from 1979 to 1992: an analysis of Multiple-Cause Mortality Data. *Ann Intern Med* 1998;129:946–953.
32. Camaschella C, Roetto A, Cali A, De Gobbi M, Garozzo G, Carella M et al. The gene *TFR2* is mutated in a new type of haemochromatosis mapping to 7q22. *Nat Genet* 2000;25:14–15.
33. Pietrangelo A, Montosi G, Totaro A, Garuti C, Conte D, Cassanelli S et al. Hereditary hemochromatosis in adults without pathogenic mutations in the hemochromatosis gene. *N Engl J Med* 1999;341:725–732.
34. Montosi G, Donovan A, Totaro A, Garuti C, Pignatti E, Cassanelli S et al. Autosomal-dominant hemochromatosis is associated with a mutation in the ferroportin (*SLC11A3*) gene. *J Clin Invest* 2001;108:619–623.
35. Njajou OT, Vaessen N, Joosse M, Berghuis B, van Dongen JW, Breuning MH et al. A mutation in *SLC11A3* is associated with autosomal dominant hemochromatosis. *Nat Genet* 2001;28:213–214.
36. Roetto A, Totaro A, Cazzola M, Cicilano M, Bosio S, D'Ascola G et al. Juvenile hemochromatosis locus maps to chromosome 1q. *Am J Hum Genet* 1999;64:1388–1393.
37. Monaghan KG, Rybicki BA, Shurafa M, Feldman GL. Mutation analysis of the *HFE* gene associated with hereditary hemochromatosis in African Americans. *Am J Hematol* 1998;58:213–217.
38. Andrews NC. Disorders of iron metabolism. *N Engl J Med* 1999;341:1986–1995.
39. De Gobbi M, Roetto A, Piperno A, Mariani R, Alberti F, Papanikolaou G et al. Natural history of juvenile hemochromatosis. *Br J Haematol* 2002;117:973–979.
40. Steinberg KK, Cogswell ME, Chang JC, Caudill SP, McQuillan GM, Bowman BA et al. Prevalence of C282Y and H63D mutations in the hemochromatosis (*HFE*) gene in the United States. *JAMA* 2001;285:2216–2222.
41. Beutler E, Felitti V, Gelbart T, Ho N. The effect of *HFE* genotypes on measurements of iron overload in patients attending a health appraisal clinic. *Ann Intern Med* 2000;133:329–337.
42. 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;343:1529–1535.
43. Powell LW, George DK, McDonnell SM, Kowdley KV. Diagnosis of hemochromatosis. *Ann Intern Med* 1998;129:925–931.
44. Beutler E, Felitti V, Koziol JA, Ho NJ, Gelbart T. Penetrance of 845G→A (C282Y) *HFE* hereditary haemochromatosis mutation in the USA. *Lancet* 2002;359:211–218.
45. Willis G, Wimperis JZ, Smith KC, Fellows IW, Jennings BA. Haemochromatosis gene C282Y homozygotes in an elderly male population. *Lancet* 1999;354:221–222.
46. Asberg A, Hveem K, Thorstensen K, Ellekjer 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;36:1108–1115.
47. US Preventive Services Task Force. Guide to clinical preventive services, 2nd ed. Baltimore: Williams & Wilkins, 1996.
48. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. *Am J Hum Genet* 1995;57:1233–1241.
49. Denayer L, Welkenhuysen M, Evers-Kiebooms G, Cassiman JJ, Van den Berghe H. Risk perception after CF carrier testing and impact of the test result on reproductive decision making. *Am J Med Genet* 1997;69:422–428.
50. Axworthy D, Brock DJ, Bobrow M, Marteau TM. Psychological impact of population-based carrier testing for cystic fibrosis: 3-year follow-up. UK Cystic Fibrosis Follow-up Study Group. *Lancet* 1996;347:1443–1446.
51. Power TE, Adams PC. Psychosocial impact of C282Y mutation testing for hemochromatosis. *Genet Test* 2001;5:107–110.
52. 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;128:370–373.
53. Kowdley KV, Hassanein T, Kaur S, Farrell FJ, Van Thiel DH, Keeffe EB et al. Primary liver cancer and survival in patients undergoing liver transplantation for hemochromatosis. *Liver Transpl Surg* 1995;1:237–241.
54. Emery J, Rose P. Hereditary haemochromatosis: never seen a case? *Br J Gen Pract* 2001;51:347–348.
55. Seamark CJ, Hutchinson M. Controversy in primary care: should asymptomatic haemochromatosis be treated? *BMJ* 2000;320:1314–1317.
56. Welch HG, Burke W. Uncertainties in genetic testing for chronic disease. *JAMA* 1998;280:1525–1527.
57. Phelps G, Chapman I, Hall P, Braund W, Mackinnon M. Prevalence of genetic haemochromatosis among diabetic patients. *Lancet* 1989;2:233–234.
58. Singh BM, Grunewald RA, Press M, Muller BR, Wise PH. Prevalence of haemochromatosis amongst patients with diabetes mellitus. *Diabet Med* 1992;9:730–731.
59. O'Brien T, Barrett B, Murray DM, Dinneen S, O'Sullivan DJ. Usefulness of biochemical screening of diabetic patients for hemochromatosis. *Diabetes Care* 1990;13:532–534.
60. Kwan T, Leber B, Ahuja S, Carter R, Gerstein HC. Patients with type 2 diabetes have a high frequency of the C282Y mutation of the hemochromatosis gene. *Clin Invest Med* 1998;21:251–257.
61. Braun J, Donner H, Plock K, Rau H, Usadel KH, Badenhoop K. Hereditary haemochromatosis mutations (*HFE*) in patients with type II diabetes mellitus. *Diabetologia* 1998;41:983–984.
62. 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;358:1405–1409.
63. Griffiths W, Cox T. Haemochromatosis: novel gene discovery and the molecular pathophysiology of iron metabolism. *Hum Mol Genet* 2000;9:2377–2382.
64. Lee PL, Gelbart T, West C, Halloran C, Felitti V, Beutler E. A study of genes that may modulate the expression of hereditary hemochromatosis: transferrin receptor-1, ferroportin, ceruloplasmin, ferritin light and heavy chains, iron regulatory proteins (IRP)-1 and -2, and hepcidin. *Blood Cells Mol Dis* 2001;27:783–802.