

Revised Report

Screening for Haemochromatosis

A report for the UK National Screening Committee

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Introduction

This report reviews screening of the UK general adult population for haemochromatosis against items 1 to 15 of the UK National Screening Committee Criteria for appraising the viability, effectiveness and appropriateness of a screening programme (National Screening Committee 2003); appraisal against the remaining items (16 to 22) appeared premature at this point.

Haemochromatosis can be broadly defined as any disorder characterized by iron deposition and tissue injury in multiple organs. It often has a hereditary component due to an autosomal recessive inherited disorder of iron metabolism which is commonest among Caucasians (Olynyk et al 2008). Genetic understanding of hereditary haemochromatosis was advanced in 1996 when two base pair alterations, termed C282Y and H63D, of the HFE gene were identified (Feder et al 1996). The availability of genotyping has made it possible to identify individuals with the susceptible genotype but with little or no evidence of disease. It is estimated that 90% of haemochromatosis among Caucasians occurs in C282Y homozygotes (Adams et al 2005). The remaining cases appear to be due to environmental factors and/or other genotypes. This review is confined to screening of the general adult population for elevated serum iron parameters and / or mutations of the HFE gene. Although haemochromatosis-related mutations of other genes have been identified they have less impact on public health and are not considered further here.

Appraisal against the NSC criteria of any proposal to screening for haemochromatosis is complicated by a lack of consensus about the condition that a screening programme should seek to detect (for example, all individuals with iron overload, or only those with iron overload attributable to one of these mutations) and the problems it should seek to prevent (for example, early symptoms attributable to iron overload, or only serious disease such as cirrhosis) (Asberg et al 2008, Waalen et al 2008).

1. The condition should be an important health problem

Individuals can be characterized in one of four general stages, with prevalence diminishing as one moves through these stages (Adams et al 2000):

- genetic predisposition without any other abnormality
- iron overload without symptoms
- iron overload with early symptoms such as fatigue
- iron overload with organ damage, especially cirrhosis

Population prevalence of the C282Y and H63D mutations in Caucasian populations has been reported in two large studies. Among 29,000 Australians, 0.68% were C282Y homozygotes and 2.4% were C282Y/H63D compound heterozygotes (Allen et al 2008). Among 44,000 non-Hispanic US whites, 0.44% were C282Y homozygotes and 2.0% were C282Y/H63D compound heterozygotes (Adams et al 2005). The latter study also found that these mutations are much less common among non-whites: only 0.14 per 1000 Blacks and fewer than 0.001 per 1000 Asians were homozygous for the C282Y mutation, and it did not account for raised blood iron indices in these racial groups. In UK studies the prevalence of C282Y homozygotes has been reported as 0.7% among Welsh blood donors (Jackson et al 2001) and 0.3% among northern English blood donors (Chambers et al 2003). The same studies reported the prevalence of C282Y/H63D compound heterozygotes as 2.4% and 2.0% respectively.

Individuals who are homozygous for the C282Y mutation are at much greater risk of developing haemochromatosis than other genotypes, and compound heterozygotes (C282Y/H63D) are at slightly increased risk (Allen et al 2008). Although some H63D homozygotes have raised serum levels of transferrin saturation (TS), the H63D mutation is probably not clinically significant in the absence of the C282Y mutation (Gochee et al 2002).

The least biased estimates of the consequences of abnormal genotype or phenotype come from cohort or cross-sectional studies and these are reviewed in the next section. However, case-control studies can give some indication of possible risks, particularly for less common outcomes. A recent meta-analysis of case-control studies that included 66,263 cases and 226,515 controls (Ellervik et al 2007) concluded that clinically ascertained C282Y homozygotes have a 4- to 11-fold risk of liver disease, whereas all 5 haemochromatosis genotypes are associated with a 2- to 48-fold risk of porphyria cutanea tarda (a photosensitive, blistering skin disease). Haemochromatosis genotypes were not associated with risk for diabetes mellitus, heart disease, arthritis, stroke, cancer, or venous disease in the overall analyses. There was a three-fold risk of diabetes mellitus among North European C282Y homozygotes; and a four-fold risk of amyotrophic lateral sclerosis (a serious but uncommon neurological disease that causes muscle weakness, disability and eventually death) among H63D homozygotes. However, these latter risks may be artefacts since they were only of borderline statistical significance; the study did not adjust for the 31 clinical end-points that were assessed; and the susceptibility of case-control studies to multiple sources of bias should be borne in mind.

On the basis that liver disease comprises the major disease burden attributable to haemochromatosis, and using the natural history data reviewed in the next section, it can be estimated that, in a cohort of 400,000 white men (approximately the annual male cohort for the UK) about 2,000 (0.5%) will be C282Y homozygotes, of whom 120 (6%) may develop cirrhosis and 20-40 (1-2%) may develop liver cancer as a result of the mutation. However, it must be emphasised that the figures for cirrhosis and liver cancer are fairly uncertain, because we still lack knowledge about the natural history of the condition.

Total all-cause mortality provides a different method for estimating the impact of haemochromatosis. Taking genotype as the starting point, the largest cohort

study (Allen et al 2008) found that the hazard ratio for death among C282Y homozygotes, as compared with subjects who had no C282Y mutation, was 1.04 (95% CI, 0.67 - 1.62). Taking phenotype as the starting point, a nationally-representative cohort study of US adults (Mainous et al 2004) found that the hazard ratio for death among the 2% of the population with a TS of > 55%, as compared with those with a TS of $\leq 55\%$, was 1.60 (95% CI, 1.17 - 2.21).

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

Biochemical expression among C282Y homozygotes appears to vary widely among individuals, and iron accumulation and disease expression are modified by environmental factors, such as blood loss from menstruation or donation, alcohol intake, diet, and comorbid disease (e.g. viral hepatitis). If symptomatic organ involvement develops, it is generally in mid-life with nonspecific signs and symptoms (e.g. unexplained fatigue, joint pain, abdominal pain). Age of onset is delayed in females, perhaps due to blood loss through menstruation. The liver is the first target organ thought to be affected by iron accumulation, which is central to both diagnosis and prognosis (Whitlock et al 2006). It is possible for C282Y homozygotes with cirrhosis to be asymptomatic (Powell et al 2006).

The risk of C282Y homozygotes developing clinical disease was assessed in a 2006 systematic review (Whitlock et al 2006). Two retrospective cohort studies and 13 cross-sectional studies met the authors' quality criteria. Combining the results of the two cohort studies (Olynyk et al 2004 - 3260 and Andersen et al 2004) yielded information on 33 C282Y homozygotes (22 women and 11 men) who were followed up for 17 to 25 years. Participants' average age at the end of observation was 47 to 63 years, though eight women (24% of those observed) were 50 years or younger at final follow-up and may not yet have reached an

age to manifest clinical expression. Among the 33 C282Y homozygotes, the frequency of various outcomes by the end of observation was as follows:

- elevated serum iron parameters (variously defined): 20–25 patients (61–75%)
- arthralgias: six patients (18%)
- diabetes: two patients (6%)
- clear evidence of liver disease: three patients (9%)

Progression of iron accumulation did not appear inevitable, particularly as measured by serum ferritin (SF), since a number of individual patients showed decreases or no change in SF levels over time, despite a lack of treatment or plausible explanation such as blood donation or loss.

A subsequent, and larger, Australian cohort study published in 2008 (Allen et al 2008, Gurrin et al 2008) followed 203 C282Y homozygotes (of whom 95 were men) aged 40–69 years at baseline, for a mean of 12 years. The group where C282Y homozygosity was clearly associated with increased risk of disease (specifically, fatigue, use of arthritis medicine or a history of liver disease) was limited to men with SF > 1000 µgram / L (37% of men and 3% of women at baseline). For C282Y homozygotes with SF of 300–1000 µg/L at baseline, the probability of progressing to SF >1000 µg/L at follow-up was 13 – 35% for men, and 16 – 22% for females (depending on the baseline TS). For C282Y homozygotes with normal baseline SF, <15% were predicted to develop SF >1000 µg/L if left untreated. This is consistent with the finding of Yamashita and Adams (2003) that among C282Y homozygotes with a normal SF level at the time of diagnosis, only 2 of 22 patients (10%) showed any significant increase in SF during a median follow-up of 4 years. Over the 12 years of follow-up in the large Australian cohort study (Allen et al 2008) 28% of men and 1% of women developed ‘disease related to iron overload’, though Waalen and Beutler (2008)

point out that only 5% of men developed more serious diseases such as cirrhosis or liver cancer.

Among the cross-sectional studies reviewed by Whitlock et al (2006), seven provided adequate data to estimate the prevalence of iron overload and disease at the time of screening in the general population (Beutler et al 2002; Burt et al 1998; Delatycki et al 2005; Deugnier et al 2002; Distante et al 1999; Olynyk et al 1999; McDonnell et al 1999). Among a total of 282 C282Y homozygotes who had not previously been identified (not all of whom were further evaluated for all outcomes) the frequency of various outcomes was as follows:

- iron overload: 38%
- liver fibrosis: 25%
- cirrhosis: 6%.

A more recent cross-sectional study (Powell et al 2006) assessed disease expression by clinical evaluation and liver biopsy in 672 essentially asymptomatic C282Y homozygous subjects identified by either family screening or health checks. The frequency of various outcomes was as follows:

- liver fibrosis: 18% of men, 5% of women
- cirrhosis: 6% of men, 2% of women.

In a Swedish population-based cohort of 1847 C282Y homozygotes (identified clinically, not through screening) the absolute risk of liver cancer after 10 years of follow-up was 6% among men and 1.5% among women (Elmberg et al 2003). The risks would be lower among C282Y homozygotes in the general population since the minority who present clinically are at higher risk of liver cancer.

Reasonable summary estimates of the proportion of male C282Y homozygotes who may develop various outcomes are given by Ayonrinde and Olynyk (2007) as follows (the corresponding figures will be substantially less for women):

- Raised serum iron indices: 61 – 75%
- Significant liver iron overload: 38%
- Liver fibrosis: 25%
- Cirrhosis: 6%
- Liver cancer: 1–2%

However, it must be emphasised that we still lack knowledge about the natural history of the condition, and will learn more as follow up continues in existing cohort studies.

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable

Reductions in population levels of alcohol consumption and obesity would plausibly reduce the disease burden associated with haemochromatosis. For the same level of hepatic iron stores, haemochromatosis patients with excessive alcohol intake are more prone to develop early and severe liver fibrosis than those who are either abstinent or light drinkers (Fletcher et al 2002). Similarly, obesity and steatosis have been associated with an increased risk of liver fibrosis in C282Y homozygotes (Powell et al 2005). Ingestion of large quantities of dietary iron and red meat in people with high TS is associated with an increase in mortality (Mainous et al 2004); while this might be relevant to individuals who know they have a high TS, a current draft UK report on iron and health does not recommend a whole-population reduction in dietary iron (Scientific Advisory Committee on Nutrition 2009) .

4 If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

About 10% of Caucasians carry the C282Y mutation and 24% carry the H63D mutation (Adams et al 2005). It is likely that only compound heterozygotes (individuals who are heterozygous for both the C282Y and the H63D mutation) are at increased risk of haemochromatosis (Allen et al 2008), though greater certainty about the risks associated with other genotypes would require larger cohort studies than have been reported.

Genotypic screening will identify carriers of the C282Y mutation, and may identify carriers of the H63D mutation (if testing for H63D forms part of the screening strategy). One Australian study tested only for the C282Y mutation, not for the H63D mutation; C282Y heterozygotes were not initially informed of their genotype, but told they were at 'low risk' and given the option of telephoning to find out if they were heterozygous or wild-type homozygous (Niselle et al 2004). A US study took the view that there may be small risks associated with a variety of genotypes other than C282Y/ C282Y, and that this necessitated telling all participants their genotype. In a follow-up survey by mail, only 75% of heterozygotes who had normal blood iron tests were confident that they did not have haemochromatosis. Participants who believed they had a mutation had worse general health and mental wellbeing than those who perceived no abnormality (Anderson et al 2006).

5 There should be a simple, safe, precise and validated screening test and

6 The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

Screening tests that have been reported in the literature assess either phenotype or genotype. Frequently used measures of phenotype are blood levels of the transferrin saturation (TS), unsaturated iron-binding capacity (UIBC) and serum ferritin (SF). Commonly used thresholds above which further evaluation may be recommended are:

- TS > 50% in men, > 45% in women
- SF > 300 µg/L in men, > 200 µg /L in women

There are no agreed reference ranges for UIBC. These tests may or may not be combined with a test for HFE genotype, which requires either a blood test or a cheek-brush or saliva test.

TS has been widely considered the preferred screening test for haemochromatosis (Adams et al 2007). However, there are a number of problems with this. An increase in total body iron burden is plausibly an important influence on liver disease and other clinical outcomes, and Beutler et al (2002) found that SF was a better predictor of total body iron burden than TS or UIBC among patients with haemochromatosis ($r^2=0.55$ for C282Y homozygotes, 0.43 for other genotypes). Adams et al (2007) identified significant within-person biological variability of TS and UIBC, so that initial screening with the commonly used thresholds for TS or UIBC missed approximately 30% of C282Y homozygotes, of whom 40% had an elevated SF. They concluded that this limits the usefulness of TS or UIBC as initial screening tests for expressing C282Y homozygotes. Data from a small Australian cohort study shows that screening with a criterion of TS>45% in early adult life could fail to detect 60% of C282Y homozygotes who subsequently develop biochemical features of haemochromatosis (Olynyk et al 2004).

A Clinical Practice Guideline from the American College of Physicians (Qaseem et al 2005) recommended that, for clinicians who choose to screen, one-time phenotypic screening of asymptomatic non-Hispanic white men with SF level and TS would have the highest yield (though it also concluded that there is insufficient evidence to recommend for or against screening for hereditary haemochromatosis in the general population).

Waaen et al (2008) argue against using TS for population screening on the grounds that the majority of subjects detected neither have clinical disease, nor

are they likely to develop it. The authors propose instead a criterion of SF > 1000 µg/L, for two reasons. First, only these patients are at risk for cirrhosis (Guyader et al 1998; Beaton et al 2002; Morrison et al 2003); second, the SF level of the majority of adult homozygotes for HFE mutations does not rise over long periods of time, so excluding subjects with SF < 1000 µg/L should not result in missed opportunities for early treatment of patients who could benefit. However, this latter assertion has been challenged by the recent large Australian cohort study, in which the probability of C282Y homozygotes progressing from SF 300–1000 µg/L at baseline to >1000 µg/L over a mean of 12 years' follow-up was 13 – 35% for men, and 16 – 22% for women (depending on the baseline TS). Even C282Y homozygotes with a normal baseline SF had up to a 15% probability of developing SF >1000 µg/L if left untreated (Gurrin et al 2008).

Asberg et al (2008) argue for initial screening with TS, followed by measurement of SF in men and women with TS > 45%. They point out that in their study four out of 12 C282Y homozygotes with liver fibrosis or cirrhosis would have been missed by this strategy if the SF cut-off were 1000 µg/L. Waalen et al (2008) suggest that these patients may have developed cirrhosis for reasons other than iron overload.

To conclude this section, there remain significant differences of opinion among experts in the field regarding which test(s), with which cut-off(s), and in what sequence, would offer the optimum trade-off between sensitivity and specificity if a general population screening programme were to be implemented. Appraisal of the sensitivity and specificity of any test, or combination of tests, for haemochromatosis is complicated by a lack of consensus about the condition that a screening programme should seek to detect (for example, all patients with iron overload, or only those with iron overload attributable to HFE mutations) and the problems it should seek to prevent (for example, all symptoms attributable to iron overload, or only serious disease such as cirrhosis) (Asberg et al 2008, Waalen et al 2008).

7 The test should be acceptable to the population

This review identified only one UK study in which a general primary care population was offered screening for haemochromatosis (Patch et al 2005). 3,000 individuals aged 30–70 were randomly selected and randomly allocated to one of two screening strategies: either phenotypic (TS measured on a blood sample taken at the GP surgery) or genotypic (on a saliva sample taken at home). Screen-positive individuals from either strategy were followed up with assessment of iron status and genotyping. Uptake was only 32% overall (though 3% higher in the genotypic than in the phenotypic strategy). Uptake was lower still (only 17%) in men aged 30–50, who would be those most with greatest potential benefit from the screening programme. The main reasons for refusal were ‘not interested’ or ‘not enough time’.

This is similar to the 28% uptake reported among 6,000 employees of an American Health Maintenance Organisation who were invited to choose screening either by TS alone or by both TS and genotyping (McDonnell et al 1999). Reasons for declining to participate were not reported.

Higher uptake was reported in a US study in which 2,165 people recruited from waiting rooms of primary care practices were randomly assigned to receive brief information on either HH genotypic or phenotypic testing (Anderson et al 2005). 56% accepted a genotypic test versus 58% for a phenotypic test (both required a blood test). Reasons for refusal included a need to talk with a doctor (44%), concern about privacy (32%), and dislike of blood-drawing (29%).

8 There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

Such a policy would depend on what test(s) and cut-off(s) have been used to define a positive result from screening. In the absence of consensus regarding

screening tests, there can be no single agreed policy on further diagnostic investigation of individuals with a 'positive' test result. The current UK guideline (British Society for Haematology 2000) gives recommendations on the diagnostic investigation of clinically suspected cases of haemochromatosis, but the appropriateness of these for a population of asymptomatic, screen-detected possible cases needs to be evaluated. The difficulties of knowing how to manage individuals with positive results are illustrated by Adams and Barton (2007) who note that assessment of mild hyperferritinaemia ($< 1000 \mu\text{g} / \text{L}$) is a common clinical problem and that many cases are unresolved because of the reluctance of patients and physicians to use liver biopsy or empirical phlebotomy as an aid to diagnosis.

9 If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

All pilots of screening for haemochromatosis that have used genotypic tests have looked for the C282Y mutation. Some, such as the small UK pilot study, have also tested for the H63D mutation (Patch et al 2005). In this study C282Y/H63D heterozygotes were defined as screen-positives 'to maximize the sensitivity of the test ... despite its low predictive value for clinically significant haemochromatosis'. This contrasts with the policy of an Australian workplace-based pilot which chose not to test for the H63D mutation, on the grounds that it would greatly reduce the positive predictive value of screening (Nissele et al 2004).

10 There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

A current UK guideline (British Society for Haematology 2000) recommends that treatment for patients with iron overload should be venesection (phlebotomy) once weekly (450–500 ml) until the SF concentration is $< 20 \text{ mg/l}$ and TS is $<$

16%. Once excess iron has been removed patients usually return to the outpatient clinic every 3 months, and further phlebotomy is carried out when necessary (up to 6 times a year).

A recent systematic review that searched for studies from 1966 to 2005 (Whitlock et al 2006) found no controlled studies of phlebotomy treatment in patients with haemochromatosis due to any cause, nor any studies that allowed comparison of early vs. delayed treatment. No such studies were identified in the course of the current review (up to December 2008).

The available treatment studies of at least fair quality are limited to four case series of referral centre patients (Bomford et al 1976; Adams et al 1991; Niederau et al 1996; Powell et al 2006). Together they describe the survival experience of 447 total patients and the reduction in morbidity after treatment of 370 haemochromatosis patients identified and treated over a 50-year period, with a mean of 14 years of follow-up. The best available evidence on the effects of phlebotomy treatment comes from pre- and post-treatment liver biopsies in 260 patients who received a diagnosis through routine clinical practice (Bomford et al 1976; Niederau et al 1996). It suggests some reversibility of hepatic disease, with 7% to 23% showing improvement and 1% to 3% showing worsening. Improvement in histologic characteristics was more common (33%) in patients with less severe, pre-cirrhotic liver disease than in patients with cirrhosis (15% improved). In a highly selected subgroup of 25 asymptomatic patients who were detected through family or health check screening, and who underwent a second biopsy after treatment, 19 of 20 showed improvement in hepatic fibrosis scores after treatment; the only case with baseline cirrhosis was unchanged (Powell et al 2006). These findings were 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) 41% of those with type 1 diabetes mellitus reduced their daily dosage; 73% with elevated liver enzymes showed improvement; and symptoms such as weakness, lethargy, or abdominal pain improved in more than half (Niederau et al 1996). Improvements in arthralgias (30%) and potency (19%) were less prominent.

One uncontrolled study asked 2851 primarily male patients with haemochromatosis 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 (McDonnell et al 1999).

To conclude this section, the available evidence on the effectiveness of phlebotomy is limited to studies with historical controls and uncontrolled before-and-after studies. This evidence has been strong enough for phlebotomy to become firmly established as standard treatment for patients with iron overload, so controlled trials of phlebotomy would not be considered ethical (British Society for Haematology 2000). However, this standard of evidence would probably not be considered adequate to justify screening asymptomatic individuals. A randomized controlled trial of screening for haemochromatosis (if one was considered justified) would provide an opportunity to compare clinical outcomes in patients who are diagnosed and treated early (as a result of screening) with outcomes in those who are diagnosed and treated later (through normal clinical practice). This would provide better-quality evidence on whether early treatment leads to better outcomes than late treatment, while avoiding the ethically unacceptable practice of withholding phlebotomy from individuals known to have haemochromatosis. However, such a trial would require a very large sample size and many years of

follow-up, and would require a degree of consensus about screening tests and thresholds that does not yet exist.

11 There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

The current UK guideline on the management of haemochromatosis (British Society for Haematology 2000) includes recommendations for the management of various categories of patients with clinically-detected haemochromatosis (depending on their levels of TS and SF, their liver iron stores and possibly liver biopsy result). To be appropriate for the management of screen-detected cases, these recommendations would need to be reviewed in the light of the evidence that has accumulated since 2000.

12 Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

One area where there may be scope for improved clinical management is in case-finding among relatives of known haemochromatosis patients. Testing of first-degree relatives of patients who present clinically with haemochromatosis would offer a much higher yield than general population screening. However, a Welsh study found that only 53% of such relatives had been tested (McCune et al 2003).

13 There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.

The effect of screening for haemochromatosis on mortality or morbidity has not been assessed in any randomised controlled trials.

14 There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

The issue of low uptake of screening for haemochromatosis has been described in section 7. Two studies suggest that compliance with phlebotomy can be high. An Australian workplace screening programme (Allen et al 2008) reported that 45 of the 47 C282Y homozygotes identified continued to access clinical care for at least 12 months, and all 22 participants requiring therapeutic phlebotomy complied with treatment for at least 12 months. A US study of patients with haemochromatosis and iron overload diagnosed during routine clinical care (not through screening) found that 84% of 142 patients complied with the first year of maintenance phlebotomy, with a further 7% annual decrease in compliance (Hicken et al 2003).

This review found no report of the views of a cross-section of health professionals on screening for haemochromatosis.

15 The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

The main potential harms reported in the literature concern psychological distress and problems with insurance. In a UK study where invitees were randomized to either a phenotypic or a genotypic screening strategy (and only 32% accepted screening), individuals completed self-rated assessments of anxiety, depression, and general health at invitation, testing, result-giving, and 6 months. There were no significant changes in the assessments over time, and no significant differences between the two screening strategies (Patch et al 2005). An Australian workplace-based pilot of cheek-brush screening for the C282Y mutation assessed anxiety before testing and 12 months after receiving results. They found a slight *decrease* in anxiety among C282Y homozygotes, including those with normal blood iron indices (Allen et al 2008). However, in a large US study that combined genotypic and phenotypic tests, individuals who received a screening result of uncertain clinical significance (an HFE mutation or somewhat elevated TS or SF) reported diminished general health and mental wellbeing, and more health worries (Anderson et al 2006). C282Y homozygotes

with transient elevations in TS or SF were approximately 20 times more likely than controls to worry about their health (Wenzel et al 2007).

Reported experiences with obtaining insurance are diverse. In one US study, 20% of 126 patients diagnosed with hereditary haemochromatosis but without end-organ damage experienced insurance denial or increased premiums (Shaheen et al 2003). A US study of insurers' responses to a dummy case of an asymptomatic man with 'gene mutations that make it likely, though not certain, he will develop hereditary haemochromatosis at some point during his lifetime' found that 20 of 23 insurers gave standard offers of cover; 2 said they were unable to offer cover without a diagnosis, and 1 refused altogether (Pollitz et al 2007). However, in a larger US / Canadian study, only three out of 832 participants who were followed up one year after they had been found to be at risk of hereditary haemochromatosis or iron overload (0.4%) had experienced problems with life insurance or long-term care insurance (Hall et al 2007). A small Australian study found that all of 32 asymptomatic subjects with HFE mutations were given insurance on standard terms, (though in one case only after intervention from the patient's doctor (Otlowski et al 2007). The Association of British Insurers' Code of Practice for Genetic Tests (ABI 2008) states that insurers may only take into account adverse results of those predictive genetic tests (i.e. taken prior to the appearance of any symptoms of the condition in question) that the government's advisory body, the Genetics and Insurance Committee (GAIC), has decided are technically, clinically and actuarially relevant. To date the GAIC has only approved one application, for Huntington's disease, for life insurance applications over £500,000, so people in the UK who are found to have a mutation that predisposes them to haemochromatosis, but who have no symptoms, should not experience insurance denial or increased premiums.

Implications for policy

Screening for haemochromatosis in the UK general adult population does not currently meet the NSC criteria. The main obstacles are a lack of consensus about the problems that screening should seek to prevent (for example, early

symptoms attributable to iron overload, or only serious disease such as cirrhosis); the lack of consensus about which test(s), with which cut-off(s), and in what sequence, should be used to define individuals as screen-positive; the low uptake of screening in pilot studies; and the lack of any randomized controlled trials to assess whether earlier treatment produces better outcomes than later treatment.

Without consensus about the problems that screening should seek to prevent, and which test(s), with which cut-off(s), and in what sequence, should be used to define individuals as screen-positive, it is difficult to appraise screening for haemochromatosis against many of the NSC criteria. If greater consensus emerges on these issues, this appraisal should be updated to give more specific answers than is possible at present.

Implications for research

If the consensus described above emerges, and an updated NSC appraisal reaches more positive conclusions about screening for haemochromatosis, an RCT would need to be conducted to confirm whether or not earlier treatment produces better outcomes. Given the long natural history of haemochromatosis, such a trial would need a long follow-up period.

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