Health Technology Assessment 2009; Vol. 13: No. 23

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April 2009
DOI: 10.3310/hta13230

Health Technology Assessment
NIHR HTA programme
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Diagnostic strategies using DNA testing for hereditary haemochromatosis in at-risk populations: a systematic review and economic evaluation

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Declared competing interests of authors: none

Published April 2009

DOI: 10.3310/hta13230

This report should be referenced as follows:

Bryant J, Cooper K, Picot J, Clegg A, Roderick P, Rosenberg W, *et al*. Diagnostic strategies using DNA testing for hereditary haemochromatosis in at-risk populations: a systematic review and economic evaluation. *Health Technol Assess* 2009;**13**(23).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (*SciSearch*®) and *Current Contents*®/Clinical Medicine.

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 05/07/04. The contractual start date was in March 2006. The draft report began editorial review in September 2007 and was accepted for publication in November 2008. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.

ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorset Press, Dorchester.

Abstract

Diagnostic strategies using DNA testing for hereditary haemochromatosis in at-risk populations: a systematic review and economic evaluation

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Objective: To evaluate DNA testing for detecting hereditary haemochromatosis (HHC) in subgroups of patients suspected of having the disorder and in family members of those diagnosed with HHC.
Data sources: Major electronic databases, searched from inception to April 2007.
Review methods: A systematic review was undertaken using a priori methods and a de novo model developed to assess costs and consequences of DNA testing.
Results: Eleven studies were identified for estimating the clinical validity of genotyping for the C282Y mutation for the diagnosis of HHC. No clinical effectiveness studies meeting the inclusion criteria were identified. Two North American cost-effectiveness studies of reasonable quality were identified but their generalisability to the UK is not clear. Three cohort studies met the inclusion criteria for the review of psychosocial aspects. All had methodological limitations and their generalisability is difficult to determine. The clinical sensitivity of C282Y homozygosity for HHC ranged from 28.4% to 100%, or from 91.3% to 92.4% when considering only the most relevant studies. Clinical specificity ranged from 98.8% to 100%. One study found that gene testing was a cost-effective method of screening relatives of patients with haemochromatosis, whereas the other found that genotyping the spouse of a homozygote was the most cost-efficient strategy. Genetic testing for haemochromatosis appears to be well accepted, is accompanied by few negative psychosocial outcomes and may lead to reduced anxiety. The de novo economic model showed that, in people suspected of having haemochromatosis, the DNA strategy is cost saving compared with the baseline strategy using liver biopsy (cost saved per case detected £123), largely because of the reduction in liver biopsies. For family testing of siblings the DNA strategy is not cost saving because of the costs of the DNA test (additional cost per case detected £200). If the cost of the test were to reduce from £100 to £60, the DNA strategy would be the cheaper one. For family testing of offspring the DNA test strategy is cheaper than the baseline biochemical testing strategy (cost saved per case detected £7982). Sensitivity analyses showed that the conclusions in each case are robust across all reasonable parameter values.
Conclusions: The preferred strategy in practice is DNA testing in conjunction with testing iron parameters when there is clear clinical indication of risk for haemochromatosis because of biochemical criteria or when there is familial risk for HHC. Access to genetic testing and centralisation of test provision in expert laboratories would lower the cost of testing, improve the cost-effectiveness of the strategy and improve the quality of information provided to clinicians and patients.

Contents

Glossary and list of abbreviations

Glossary

ACCE A model process for evaluating data on emerging genetic tests. It takes its name from the four components of evaluation – *A*nalytical validity, *C*linical validity, *C*linical utility and associated *E*thical, legal and social implications.

C282Y Mutation in the HFE protein that results from a G to A transition at nucleotide 845 of the *HFE* gene, which produces a substitution of cysteine (C) for tyrosine (Y) at amino acid position 282 in the protein product.

H63D Mutation in the HFE protein that results from a C to G transition at nucleotide 187 of the *HFE* gene causing an aspartate (D) to substitute for histidine (H) at position 63 in the HFE protein.

HFE Haemochromatosis gene [found in region 21.3 on the short (p) arm of human chromosome 6] or the protein encoded by the gene ('high Fe').

HLA-A3 Human histocompatibility (HLA) surface antigen encoded by the A locus on chromosome 6.

HLA-H Alternative symbol for *HFE* gene.

S65C Mutation in the HFE protein that results from an A to T transition at nucleotide 193 of the *HFE* gene which produces a substitution of serine (S) for cysteine (C) at amino acid position 65 in the protein product.

YD Compound heterozygous, C282Y/H63D

YY Homozygous, C282Y/C282Y

List of abbreviations

µg Fe/g	micrograms of iron per gram of tissue
BSH	British Society for Haematology
DARE	Database of Abstracts of Reviews of Effectiveness
DMT1	divalent metal transporter 1 protein
ECG	electrocardiogram
HC	haemochromatosis (phenotype)
HHC	hereditary haemochromatosis (due to mutation of *HFE* gene)
HI (µg/year)	hepatic iron, micrograms per year
HII	hepatic iron index
HLA	human leucocyte antigen
HTA	Health Technology Assessment
IES	Impact of Event Scale
LIC	liver iron content
LYS	life-years saved
MCS	mental component score of SF-36

MEDION	*Me*ta-analyses von *Di*agnostisch *On*derzoek
NHS EED	NHS Economic Evaluations Database
NICE	National Institute for Health and Clinical Excellence
NPV	negative predictive value
NR	not reported
NRR	National Research Register
PCR	polymerase chain reaction
PCS	physical component score of SF-36
PPV	positive predictive value
PSA	probabilistic sensitivity analysis
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	randomised controlled trial
RFLP	restriction fragment length polymorphism
SCI	Science Citation Index
SD	standard deviation
SEM	standard error of the mean
SF	serum ferritin
SF-36	Short-Form 36 Health Survey
SHTAC	Southampton Health Technology Assessments Centre
SSCP	single-strand conformation polymorphism
SSCP-CE	single-strand conformation polymorphism analysis for capillary electrophoresis
STAI-State	Spielberger State–Trait Anxiety Inventory
TS	transferrin saturation
UKGTN	UK Genetic Testing Network
wt	wild type

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Hereditary haemochromatosis is an autosomal recessive disorder of iron metabolism that leads to excessive iron absorption and progressive abnormal deposition of iron in vital organs. A common causative mutation has been identified but not all homozygotes for the mutation will develop the phenotypic expression of the condition. Treatment by phlebotomy is simple and effective. The best diagnostic strategy for detecting hereditary haemochromatosis using DNA testing is unclear.

Objective

The main aim of this study was to evaluate the use of DNA testing for detecting hereditary haemochromatosis in subgroups of patients suspected of having the disorder on the basis of clinical presentation and disturbed iron parameters, and in family members of those diagnosed with haemochromatosis.

Methods

A systematic review of the evidence was undertaken using a priori methods. A de novo model was developed to assess costs and consequences of DNA testing.

Data sources

Fifteen electronic databases were searched from inception to April 2007. Bibliographies of related papers were assessed for relevant studies and experts contacted to identify additional published references.

Study selection

Studies were included if they fulfilled the following criteria:

- Intervention:
  - DNA tests.
- Participants:
  - clinical validity – Caucasians with signs and symptoms suggestive of haemochromatosis
  - clinical utility – Caucasians with signs and symptoms suggestive of haemochromatosis and/or relatives of suspected cases
  - psychosocial aspects – diagnosed and at-risk individuals.
- Comparator:
  - clinical validity – control population
  - clinical utility – any case identification strategy not involving DNA testing.
- Outcomes:
  - clinical validity – sensitivity and specificity
  - clinical utility – treatment, morbidity, mortality, quality of life, psychosocial aspects, cost per case detected, cost-effectiveness or cost–utility
  - psychosocial aspects – treatment compliance, psychological outcomes, legal implications, quality of life, discrimination/stigmatisation.
- Design:
  - clinical validity – controlled cohort or case–control
  - clinical utility – randomised controlled trials, cohorts with controls, case–control, economic evaluations, modelling studies
  - psychosocial aspects – any quantitative or qualitative primary research.

Studies identified were assessed for inclusion through two stages with titles and abstracts and full papers of retrieved studies assessed independently by two reviewers, with differences in decisions resolved through discussion or through recourse to a third independent reviewer.

Data extraction and quality assessment

Data were extracted by two reviewers using a data extraction form developed a priori. Any disagreements were resolved through discussion or through recourse to independent assessment by a third reviewer. The methodological quality of the studies included in the systematic review was assessed using modified quality assessment tools using individual components of methodological

quality rather than relying on summary scores. The quality criteria were applied by two reviewers, with any disagreements resolved through discussion or through recourse to a third independent reviewer.

Data synthesis

Studies were synthesised using a narrative approach with full tabulation of results from all included studies.

Economic model

The economic evaluation developed two decision-analytic models to compare the costs and consequences of diagnostic strategies with and without DNA testing: one for people suspected of having haemochromatosis and the second for family members of patients diagnosed with haemochromatosis. Structure and data inputs of the decision trees were informed by systematic reviews and systematic searches of the literature and discussion with experts. Costs were derived from published primary data and from national and local NHS unit costs. The outcome reported is cost per case detected.

Results

Number and quality of studies

Eleven studies were identified that could be used to estimate the clinical validity of genotyping for the C282Y mutation for the diagnosis of hereditary haemochromatosis. The quality of the studies was variable and a range of definitions for the clinical phenotype was used. No clinical effectiveness studies meeting the inclusion criteria for the review were identified. Two cost-effectiveness studies (one cost–utility model and one cost-minimisation model) conducted in North America were identified. Both were of reasonable quality but their generalisability to the UK is not clear. Three cohort studies met the inclusion criteria for the review of psychosocial aspects. Each study assessed and reported on the psychosocial outcomes of genetic testing in a different way. All had methodological limitations and the generalisability of these studies is difficult to determine.

Summary of clinical validity and clinical utility

The clinical sensitivity of C282Y homozygosity for hereditary haemochromatosis ranged from 28.4% to 100% in the eleven studies; when considering only the most relevant studies, sensitivity ranged from 91.3% to 92.4%. Clinical specificity ranged from 98.8% to 100%. One cost-effectiveness study found that gene testing was a cost-effective method of screening relatives of patients with haemochromatosis, whereas the other study found that genotyping the spouse of a homozygote was the most cost-efficient strategy in family testing.

Summary of psychosocial aspects of DNA testing

Generally the results suggest that genetic testing in the case of haemochromatosis is well accepted, is accompanied by few negative psychosocial outcomes and may lead to reduced anxiety. Control subjects in the one study that had a control group anticipated greater anxiety, depression, anger and difficulty in affording the genetic test than was reported by patients. In one study clinically affected participants had significantly lower health-related quality of life, as measured by the Short-Form 36 Health Survey (SF-36) physical component summary, before genetic testing than unaffected participants but this was no longer significantly different at 12 months post consultation. Another study reported significant improvements in the vitality subscale of the SF-36 health measure and the physical composite score after participants were informed of their genetic test result. For generalised anxiety scores or intrusive thoughts, one study reported no statistically significant differences between clinically affected and unaffected participants before and after genetic testing; another study reported that anxiety fell significantly in C282Y homozygotes and heterozygotes once they received their genetic testing results.

Summary of economic evaluation

The de novo economic model demonstrated that, for people suspected of having haemochromatosis, the DNA strategy is cost saving compared with the baseline strategy using liver biopsy (cost saved per case detected £123). This is largely because of cost savings from the reduced number of liver biopsies being performed. For family testing, the DNA strategy is not cost saving in the case of siblings because of the extra costs of the DNA test (additional cost per case detected £200). If the cost of the DNA test were to fall from £100 to £60, the DNA strategy would be the cheaper one. For family testing of offspring of people with hereditary haemochromatosis, the DNA test strategy is cheaper than the baseline biochemical testing

strategy (cost saved per case detected £7982). Sensitivity analyses show that the conclusions in each case are robust across all reasonable parameter values.

Results suggest that using a diagnostic strategy that incorporates DNA testing is cost saving in case identification and in testing offspring of haemochromatosis patients. The results for siblings suggest that DNA testing is not cost saving. However, this study considered cost per case detected and it was not possible to incorporate the benefit of reassurance and reduction in anxiety resulting from DNA testing, which could have an impact on the long-term cost-effectiveness of DNA testing in siblings.

Conclusions

Implications for service provision

The preferred strategy in practice is DNA testing in conjunction with testing iron parameters when there is a clear clinical indication of suspicion of risk for haemochromatosis because of biochemical criteria or when there is a familial risk for hereditary haemochromatosis. Although clinical practice among those expert and interested in the management of the condition is already thought to follow this strategy, the development and dissemination of guidelines to physicians in both primary and secondary care is advisable. Access to genetic testing and centralisation of test provision in expert laboratories would lower the cost of testing, improve the cost-effectiveness of the strategy and improve the quality of information provided to clinicians and patients.

Suggested research priorities

The limited evidence base for assessing the use of DNA testing for haemochromatosis suggests that further primary research in the form of prospective long-term follow-up studies is required. However, an area of research more likely to be of practical value is epidemiological research, using national databases, on the environmental and other genetic factors that affect the penetrance of the genetic mutation to identify those people homozygous for the mutation who are likely to develop iron overload. Further research into psychosocial aspects of the use of DNA testing for haemochromatosis might be required after other factors that influence the expression of the phenotype have been identified.

Chapter 1
Background

Description of the health problem

Hereditary haemochromatosis (HHC) results from a genetic disorder of iron metabolism that leads to excessive intestinal absorption of iron and a progressive abnormal deposition of iron in the liver, heart, pancreas and other vital organs. Iron levels in the body are usually carefully regulated. Iron is absorbed from dietary sources to maintain iron stores and replace iron that is lost daily, mostly because of the loss of iron-containing red blood cells into the gut. In younger women, menstruation also makes an important contribution to iron loss. Haemochromatosis (the clinical condition of iron overload) occurs when this careful regulation of iron is gradually lost. In HHC absorption of iron from the gastrointestinal tract continues to occur when bodily iron stores and blood iron levels have reached and then exceeded normal levels, and iron therefore continues to accumulate within cells. Treatment by removing excess iron with phlebotomy is effective and, if started before irreversible end-organ damage, restores normal life expectancy.[1,2]

Haemochromatosis was first identified in the late nineteenth century as the classic clinical triad of diabetes, bronze skin pigmentation and liver cirrhosis (cited in Sheldon[3]). The condition was recognised as an inborn error of iron metabolism with a possible familial component in the 1930s.[3,4] In 1976 the demonstration of an excess of human leucocyte antigen (HLA)-A3 alleles in individuals with haemochromatosis compared with the normal population led to the conclusion that haemochromatosis was caused by an undefined gene that was tightly linked to the HLA locus on chromosome 6.[5] Despite this relatively early success of linkage methods for suggesting the chromosomal location of a disease gene, it took a further 20 years before, in 1996, the causative gene was identified through classic positional cloning techniques.[6,7] It is now recognised that HHC is an autosomal recessive disorder resulting from mutations of the *HFE* gene, usually manifesting in adults in their 40s and 50s.[6]

Genetic studies have shown that the mutations associated with a risk of HHC are common (see section on epidemiology). However, there is debate in the clinical literature about the clinical expression of the condition.[6,8] Of particular importance is the penetrance of the gene mutations, that is, the probability that a person with the gene mutations will develop clinical consequences (disease). Penetrance has been reported to be less than 1%[9] or as high as 40% in male relatives of affected individuals.[10] It is now clear that the at-risk genotype is a necessary but not sufficient cause of disease and that a range of factors determine the extent to which the phenotype is observed in a particular individual. Although the frequency of the genetic predisposition is the same in men and women, women have a lower incidence of the clinical phenotype. The explanation is probably that women lose iron through physiological blood loss (menstruation, childbirth) until they are postmenopausal. Phenotypic expression of haemochromatosis is variable and appears to depend on a complex interplay of the status of the *HFE* gene, other genetic factors, age, sex and such environmental influences as dietary iron, the extent of iron losses from other processes and the presence of other diseases or toxins (e.g. alcohol). There is agreement that the clinical condition of haemochromatosis is the end result of a combination of genetic and environmental factors, not all of which have been described.

The discovery of the *HFE* gene in 1996[6] has led to increasing interest in haemochromatosis and the possibility of using DNA-based predisposition testing as a tool for diagnosis and family testing. The purpose of testing is case identification and the identification of children and siblings who are at increased risk for the disease, as early identification of iron overload and initiation of treatment is considered to be effective.[11] Although the mutations associated with a risk of HHC are a good diagnostic indicator in those already suspected of having haemochromatosis or in the context of family testing, they are not useful for screening at the population level. The high prevalence of the genetic predisposition, the preventable serious consequences of progressive iron overload and the availability of effective treatment have been put forward as arguments for population screening in line with the World Health

Organization criteria,[12] but recent guidelines have suggested that the natural history and penetrance of the condition is not clearly enough understood to recommend screening programmes based on genotype or phenotype.[13,14]

Iron metabolism

Iron is vital for all living organisms as it is an essential component of a wide variety of metabolic reactions including transport of oxygen, DNA synthesis and electron transport. However, iron concentrations in the tissue need to be tightly regulated as excessive iron is toxic as a result of the formation of free radicals. The control of iron uptake and storage is therefore complex.

The majority of total body iron (60–70%) is present in haemoglobin in the erythrocyte pool. Another 10% is present in the form of myoglobins, cytochromes and iron-containing enzymes and, in a healthy individual, the remaining storage iron is sequestered by ferritin and haemosiderin in the liver, spleen and bone marrow. There is a constant turnover of iron for haemoglobin synthesis by erythroid precursor cells in the bone marrow; the majority of iron for this is recovered from the destruction of red blood cells. Iron is transported in the blood tightly bound to transferrin and, although this is less than 1% of the total body iron store, because of its high turnover it is the most significant body iron pool.[15–18]

A constant balance between uptake, transport, utilisation and storage of iron is needed to maintain cellular iron homeostasis both at the level of the cell and at the level of the whole organism. Identification of the gene for HHC has led to increased understanding of the biological pathways underpinning this process. This tight regulation depends upon the constant movement of iron bound to transferrin in the plasma between the functional iron pool and the storage iron pool. Because of its low solubility iron is not excreted, although iron is lost through menstruation, other blood loss and shedding of epithelial cells from the gastrointestinal and urogenital systems and the skin. The primary level at which body iron content is controlled is by variation in the amount of iron absorbed from the diet at the level of the small intestine.

Iron is transported across the apical cell membrane of duodenal epithelial cells by the divalent metal transporter 1 (DMT1) protein. It is then either stored as ferritin or exported by ferroportin across the basolateral membrane where it enters the circulation bound by transferrin. Both DMT1 and ferroportin expression are dependent on cellular iron stores. In haemochromatosis duodenal DMT1 and ferroportin expression are raised, leading to excess iron absorption and gradual accumulation of iron.[18–20]

The recently identified protein hepcidin is central to the pathophysiology of haemochromatosis. Hepcidin is a circulating hormone synthesised in the liver and levels of expression are regulated by iron stores and inflammation. Hepcidin is upregulated in the presence of iron and acts on ferroportin to inhibit iron transport, presumably resulting in decreased iron absorption.[21] In HHC hepcidin levels are inappropriately low.

Clinical features of haemochromatosis

Symptoms of disease

In the early stages HHC is usually asymptomatic but as excess iron continues to be deposited damage begins to occur in a wide range of organs. Initial symptoms such as fatigue, joint pain, abdominal pain or sexual dysfunction[22,23] are non-specific and may often be ignored or misdiagnosed. Clinical findings include abnormal liver function tests, diabetes and electrocardiogram (ECG) abnormalities. In men, clinical signs of haemochromatosis usually become overt in the fourth or fifth decade of life. Women may present later in life, because the loss of iron during menstruation and pregnancy confers some degree of protection against the process of iron accumulation over time. A comparison of male and female patients with diagnosed haemochromatosis, however, suggests that in women full phenotypic expression can be seen.[24] The non-specific nature of the early signs and symptoms of haemochromatosis leads to problems in diagnosis. As many of these early signs and symptoms are common they have low positive predictive value (PPV) for a diagnosis of haemochromatosis, which is a condition of low clinical prevalence.

Liver

The liver is one of the most common organs to be affected and hepatomegaly (enlargement) is one of the most frequent findings at clinical presentation.[25] It is assumed that progressive iron overload leads to liver fibrosis and ultimately cirrhosis. The percentage of patients who are reported to have cirrhosis at the time of presentation varies but there is a suggestion that it

is reducing over time, possibly because of earlier referral and diagnosis. The presence of cirrhosis at diagnosis is predictive of poorer survival.[1,26,27]

There is up to a 200-fold increased risk of hepatocellular carcinoma in patients with haemochromatosis.[26,28] Studies of patients having liver transplants suggest that undiagnosed haemochromatosis is not infrequent, that the occurrence of unsuspected hepatocellular carcinoma in this group is increased, and that life expectancy post transplant for patients with undiagnosed haemochromatosis is significantly reduced.[29,30]

In addition to hepatocellular carcinoma the fibrosis and cirrhosis caused by progressive iron overload will be a cause of progressive liver disease with the attendant morbidity and mortality.

Arthropathy
Arthropathy presents with bony swellings of the joints and may resemble osteoarthritis. Characteristically the second and third metacarpal joints are affected but all joints may be involved, particularly the wrists, ankles and knees.
The pathophysiology of the arthropathy of haemochromatosis is not characterised,[31] although there is evidence of iron deposition in the articular cartilage of patients with haemochromatosis.[32] Arthropathies are found in 40–75% of patients,[22] but the occurrence may be overestimated as arthritis is a common symptom; estimates are usually based on patient information, and the actual site and severity of the arthropathy is often not characterised. Arthritis as a symptom of haemochromatosis appears to be associated with a reduced quality of life[33] and unfortunately is one of the symptoms that is probably not improved by venesection therapy and which may in fact deteriorate in some patients.[1,34]

Endocrine
Diabetes mellitus is the major endocrine disorder associated with haemochromatosis. There are probably two distinct mechanisms: first, iron accumulation in the pancreatic β-cells leading to decreased insulin production and, second, iron accumulation in other tissues, which impairs insulin sensitivity.[26] The same issues regarding the prevalence of cirrhosis at diagnosis apply to the changing prevalence of diabetes over time. The changing testing and referral patterns may result in the diagnosis and treatment of a group of patients who would not develop serious disease, rather than reducing the incidence of serious disease by early treatment.

Hypogonadism also occurs and is caused primarily by gonadotropin deficiency resulting from iron deposition in the pituitary or hypothalamus. Other endocrine disorders including impairment of the thyroid, parathyroid or adrenal glands have been reported.

Heart
Cardiac manifestations of haemochromatosis are thought to be associated with iron deposition in the myocardium. Congestive heart failure and arrhythmias have been seen in 2–35% and 7–36% of HHC patients respectively.[35] ECG abnormalities have been reported to be more common in patients than in control subjects and it is suggested that abnormalities of cardiac conduction precede the development of cardiomyopathy and may be reversible by treatment.[36]

Genetics of haemochromatosis

Two missense mutations of the *HFE* gene were identified in 1996[6] and the relationship between these two common mutations and haemochromatosis has been subsequently confirmed in prevalence studies (see section on epidemiology). The major mutation is characterised by a G to A transition at nucleotide 845 causing tyrosine to substitute for cysteine at position 282 in the HFE protein (C282Y). The second mutation is a C to G transition at nucleotide 187 causing a histidine to aspartate substitution at position 63 (H63D).

The majority of patients are homozygous for the C282Y mutation, with a smaller minority compound heterozygotes for both mutations.[6,37–39] The significance of the H63D mutation is unclear.[6,40] Although the H63D mutation does increase transferrin saturation (TS) and ferritin levels in population samples, it is thought that compound heterozygosity is not sufficient for the development of clinically diagnosed haemochromatosis in isolation, although it may confer excess risk in the presence of other contributory factors such as alcoholic liver disease.[41–43] The frequency of compound heterozygosity is no higher in cases of haemochromatosis than in the general population.[38,44]

The discovery of the *HFE* gene has facilitated understanding of the basic mechanisms underpinning the development of haemochromatosis as well as pushing forward the understanding of iron metabolism in general. Since the discovery of the *HFE* gene a number of mutations of other genes have been discovered that also cause haemochromatosis.[45–48] However, these are individually rare and mutation testing is not routinely undertaken outside of research settings. This report will focus on the commonest (classic) form of HHC, linked to mutations in the *HFE* gene (HHC type 1), and specifically homozygosity for the C282Y mutation.

Laboratory testing for iron

Serum iron, total iron binding capacity and transferrin saturation

Measurement of serum iron alone is of little clinical use as there is considerable variation from hour to hour in normal individuals. More information is obtained by measuring serum iron concentration and total iron-binding capacity (serum iron plus unbound iron-binding capacity) as a surrogate for percentage saturation of transferrin. Transferrin may also be measured by immunological methods and TS calculated directly {TS = [serum iron/total iron-binding capacity]×100 or [serum iron/(serum iron×unsaturated iron-binding capacity)]×100}. TS is considered the 'gold standard' for assessment of iron overload; however, there remain issues relating to test standards and quality control, whichever technique is used, and problems with standardisation of these assays are recognised.[17,49] TS can also be decreased in inflammatory states, can be increased by alcohol consumption and can be artefactually changed by recent ingestion of iron or vitamins.

Serum ferritin (SF) is considered to correlate with the total amount of storage iron in normal individuals. Iron overload is correlated with a high SF; however, SF may also be high in other forms of liver disease, cancer, infection, inflammation and chronic disease.[17]

Quantitative phlebotomy

This is used to measure iron stores. It provides a direct measurement of the amount of iron available for haemoglobin synthesis. Blood is removed weekly and after a number of venesections the patient is unable to maintain his or her normal haemoglobin level. At this point it is assumed that the available iron stores have been used and the amount of iron removed can be calculated, although there is no gold standard against which this can be evaluated. Individuals with normal iron stores become iron deficient after the removal of approximately 1.5–2 g of iron (i.e. four 500-ml units of blood).[17] Individuals with iron overload will require more venesections to deplete their storage iron.[50]

Liver biopsy

Liver biopsy was the definitive test for a diagnosis of haemochromatosis and allows histochemical estimation of tissue iron, assessment of the extent of fibrosis or cirrhosis and chemical measurement of hepatic iron concentration. The degree of stainable liver iron is usually graded and the consensus is that grades 0–1 are normal and grades 2–4 represent increased parenchymal iron stores. Iron deposition in the liver may be increased in various forms of liver disease including alcoholic cirrhosis.

It has been accepted that a hepatic iron index (hepatic iron concentration divided by age) greater than 1.9 discriminates between hepatic iron overload caused by HHC and hepatic iron overload caused by other liver diseases. This is based on the concept that iron overload increases with age in haemochromatosis but is stable in other chronic liver diseases. A hepatic iron index greater than 1.9 was considered to be the gold standard test for haemochromatosis.[50,51] The identification of the genetic basis of haemochromatosis now means that the role of liver biopsy in the diagnostic pathway is being reduced.[52]

Non-invasive imaging, such as magnetic resonance imaging or computerised tomography scans, are not widely recommended for diagnostic purposes.

Treatment of haemochromatosis

Venesection as a therapy for haemochromatosis is considered to be safe, inexpensive and effective. Practice guidelines suggest removal of iron by weekly or twice-weekly phlebotomy until the patient is marginally iron deficient. Subsequently the frequency of phlebotomy is adjusted according to serum TS and SF levels.[53]

Evidence for the benefits of treatment comes from observational studies, including a small study that compared a series of treated patients with current and historical control subjects untreated either because they refused treatment or because they were diagnosed before venesection was a recognised treatment.[54] This study indicated a benefit of treatment with prolonged survival and a reduction in signs and symptoms in the treated group. As there was no random allocation of treatment, these results may be confounded by systematic differences between the treated and untreated groups.

The most widely reported evidence for the benefits of treatment comes from a cohort of patients referred to a specialist German centre together with family members identified through family screening.[1] Analysis of the outcomes in these patients suggests that if treatment is initiated before the development of irreversible cirrhosis, diabetes or cardiomyopathy, then mortality in the treated group is no different from mortality in the population from which they are derived, when making comparisons using population mortality data. However, although this study uses age- and sex-matched data as a control, there is no concurrent control group and it cannot be assumed that 100% of the group who were diagnosed without symptoms would have developed serious complications of the condition. Similar findings of the benefit of treatment have been reported from other studies.[2,26,27] It would now be unethical to conduct a randomised controlled trial (RCT) of treatment versus non-treatment as the evidence is strongly suggestive of the benefit of treatment in individuals diagnosed clinically and patients report symptomatic improvement.

In a postal survey of diagnosed patients 86% reported that some or all of their symptoms improved with therapy.[34] In patients with established iron overload and symptomatic disease, liver function, weakness, fatigue, loss of libido, cardiomyopathy and skin pigmentation usually improve.[55] As discussed previously, the response to treatment for arthritis is variable. Removal of excess iron does not reverse cirrhosis or diabetes but the latter can be stabilised and insulin requirements reduced.[1,54]

Although venesection as a therapy for preventing the complications of haemochromatosis is considered to be simple, the patient perspective has not been evaluated. One anecdotal report suggests that the adverse effects of treatment may not be as trivial as is usually assumed.[56,57] In a postal survey 12% of patients expressed a negative attitude towards phlebotomy, citing problems with venous access and the time involved and also dissatisfaction that the blood was discarded.[34] Initial compliance with therapy appears to be good; however, over the long term compliance may decline.[58]

Some questions remain around when to start treatment, for instance should C282Y homozygotes with raised TS and a normal SF be given treatment? The British Society for Haematology (BSH) guidelines on haemochromatosis state that treatment would not normally be given at that stage of iron accumulation. For those with normal values of TS and SF concentration no treatment is necessary. The guidelines suggest that it would be reasonable to monitor iron status at yearly intervals to detect when SF becomes raised, indicating the onset of tissue iron accumulation.

Epidemiology

Hereditary haemochromatosis is a common inherited metabolic disorder that predominantly affects Caucasian populations of north European descent, particularly those of Celtic origin.[59] Although several genetic and environmental factors are thought to affect the development of haemochromatosis, the existence of the C282Y and H63D mutations on the *HFE* gene underlie the disease.[59–61] However, as previously discussed, the significance of the H63D mutation is not clear. As early treatment through phlebotomy may prevent premature illness and death,[60] it is important to identify the most effective strategies for diagnosing the condition as early as possible. Given the apparent significance of the genetic component of haemochromatosis, it is necessary to assess the prevalence of the genetic mutations, the penetrance of the condition and the prevalence of the condition itself to adequately assess the effectiveness of different diagnostic strategies; however, difficulties exist in identifying reliable data. Assessment has tended to rely on the use of cohort studies of different population groups. These may be affected by certain limitations. Several studies use information from registers of particular health service users, which may not be representative of the general population (e.g. healthy blood donors).[61] Studies focusing on people with haemochromatosis may be affected

by the differing definitions and diagnostic criteria used to identify the condition and its sufferers.[13,38,62] Other studies have focused on populations with differing ethnic groups, which considering the genetic nature of this condition may affect any epidemiological data.[61] Similarly, demographic and environmental factors may influence the development of haemochromatosis and so any variations in these factors may limit the comparability of studies. Notwithstanding these difficulties, several studies have been undertaken within the UK and Ireland that provide an indication of the prevalence of the genetic mutation and the disease, as well as the penetrance of the condition. The following sections discuss these studies, outlining their key characteristics and their findings.

UK epidemiology studies

Eight studies have been included in the assessment of the prevalence of the key genetic mutations within the general population and among those with haemochromatosis in the UK, Jersey and Ireland (*Table 1* and see Chapter 3).[13,38,62–67] Six studies were prospective cohort studies,[38,62,63,65–67] with two including a control group.[38,62] The other two studies were a retrospective cohort study[13] and a cross-sectional case–control study.[64] The participants in the studies varied depending upon the rationale for the study, including people diagnosed with haemochromatosis,[13,38,62] people attending a blood donation service,[65,67] those on registers of newborn children[63] or heart attack sufferers,[64] and those attending for routine blood screening.[66] Control groups included healthy

TABLE 1 *Characteristics of included prevalence studies*

		Populations	
Study	**Design**	**General population cohorts**	**Control group**
Byrnes *et al*. 2001; [63] Ireland	Prospective cohort study	Randomly selected cohort from register of newborn children with Irish native surnames ($n = 800$)	None
Jackson *et al*. 2001;[65] Wales	Prospective cohort study	People (mean age 37.8 years men/35.7 years women) attending a blood donation service ($n = 10{,}556$)	None
Merryweather-Clarke *et al*. 1998;[67] Jersey	Prospective cohort study	Volunteer blood donors ($n = 411$)	None
		Specific non-HHC patient groups	**Control group**
O'Hara *et al*. 2003;[66] Ireland	Prospective cohort study	A cohort of inpatients, outpatients and general practice referrals providing fasting blood specimens to laboratory for routine screening ($n = 330$; mean age 56.5 years men/61.8 years women)	None
Campbell *et al*. 2003;[64] Scotland	Cross-sectional case–control study	Patients aged 25–64 on the MONICA heart attack register who had survived a first myocardial infarction ($n = 924$)	Patients aged 55–74 years chosen at random from general practitioner registers ($n = 1009$)
		HHC patient groups	**Control group**
UK HHC Consortium 1997;[38] England and Wales	Prospective cohort and control study	Multicentre cohort of people from England and Wales with HHC diagnosed through hepatic iron index > 1.9 or > 5 g mobilisable iron from quantitative phlebotomy in absence of other cause of iron overload ($n = 115$)	Healthy blood donors from Wales ($n = 101$)
Murphy *et al*. 1998;[62] Northern Ireland	Prospective cohort and control study	A selected cohort of people diagnosed with HHC through pathology and liver biopsy ($n = 30$)	People on bone marrow register ($n = 404$)
McCune *et al*. 2002;[13] Wales	Retrospective cohort study	People (mean age 49.1 years men/51.3 years women) diagnosed and treated for HHC. Diagnosed on iron indices above normal range for hospital on two occasions and no other causes ($n = 81$)	None

MONICA, Multinational Monitoring of Trends and Determinants in Cardiovascular Disease.

blood donors,[38] people registered with general practitioners[64] and people on bone marrow registers.[62]

Prevalence of the genetic mutations in the general population

The prevalence of the genetic mutations in the general population appears to vary, with rates differing depending on the specific mutation, whether homozygous, heterozygous, wild type or compound heterozygous and the characteristics of the study and its population (*Table 2*). Prevalence data for the general population originated from several cohorts including healthy blood donors,[38,65,67] a register of newborn children,[63] general practitioner populations,[64] people on bone

TABLE 2 *Prevalence of the C282Y and H63D genetic mutations in UK and Ireland populations*

Genotype	General population	Patients with HHC
C282Y homozygous	0.9%[64]	
	0.68%[65]	
	0.97%[67]	
	0.99%[38]	91.3%[38]
	1.0%[63]	
	0.93%[66]	
	1.24%[62]	90%[62]
		72.8%[13a]
C282Y heterozygous	15.3%[64]	
	12.7%[65]	
	11.4%[67]	
	5.9%[38]	0.87%[38]
	19%[63]	
		2.5%[13a]
H63D homozygous	2.1%[64]	
	2.4%[65]	
	2.9%[67]	
	2.97%[38]	0.87%[38]
	1.0%[63]	
		1.2%[13a]
H63D heterozygous	25.2%[64]	
	23.6%[65]	
	20.9%[67]	
	21.8%[38]	0[38]
	28%[63]	
Compound heterozygous (C282Y/H63D)	2.4%[64]	
	2.4%[65]	
	3.2%[67]	
	3.96%[38]	2.6%[38]
	4.0%[63]	
		7.4%[13a]
Wild type	58.3%[65]	
	60.6%[67]	
	64.4%[38]	4.4%[38]

a 16.1% of the study population not genotyped.

marrow registers[62] and people providing blood specimens for routine screening.[66] Inevitably the variations in these groups may have some effect on the prevalence rates reported. In the UK studies identified, the prevalence of the C282Y homozygous mutation in the general population ranged from 0.68%[65] to 1.24%,[62] with five studies identifying prevalence rates between 0.9% and 1% (median prevalence 0.97%).[38,63,64,66,67] Prevalence rates in the UK for the C282Y heterozygous mutation were higher and had a wider range. The prevalence in the five studies ranged from 5.9% in a cohort of healthy blood donors[38] to 19% in a cohort of newborn Irish children.[63] The median prevalence for the C282Y heterozygous mutation was 12.7%, reported in a cohort attending a blood donation service.[65] The prevalence of the H63D mutation was higher than the prevalence of the C282Y mutation in the general population of the UK, although rates also varied among the studies. In the five studies assessing the general population, prevalence of the H63D homozygous mutation in cohorts in the UK and Ireland rates ranged from 1.0%[63] to 2.97%[38] (median prevalence of 2.4%[65]). Prevalence rates for the H63D heterozygous mutation ranged from 20.9%[67] to 28%[63] in studies examining cohorts in the general population (median prevalence 23.2%[64]). The compound heterozygous mutation (C282Y/H63D) was less prevalent in the general population than the C282Y heterozygous and H63D heterozygous mutations with rates varying from 2.4%[64,65] to 4.0%[63] (median prevalence 3.2%[67]). The prevalence of the wild-type genotype in the general population cohorts ranged from 58.3%[65] to 64.4%[38] (median 60.6%[67]).

Prevalence of the genetic mutations in people with haemochromatosis

Three studies assessed the prevalence of the different genetic mutations in people with haemochromatosis in the UK and Ireland.[13,38,62] Inevitably variation in the prevalence of the genetic mutations may encompass some of the differences in the diagnostic criteria used by the studies to identify people with haemochromatosis. Unsurprisingly, the prevalence of these mutations varied considerably from the prevalence in the general population. The prevalence of the C282Y homozygous mutation was higher among those people with haemochromatosis than in the general population, with rates varying from 72.8%[13] to 91.3%.[38] The prevalence reported by McCune and colleagues[13] was considerably lower than the median prevalence for the three studies of 90%.[13,38,62] This may reflect the fact that 16% of patients in the study by McCune and colleagues were not genotyped.[13] The comparatively high prevalence of the C282Y homozygous mutation among those people with haemochromatosis reflects the underlying importance of this mutation in people developing the phenotype. In contrast, the prevalence of the C282Y heterozygous mutation was lower than that for the general population. The prevalence was reported by two studies with rates ranging from 0.87%[38] to 2.5%.[13] For the H63D genetic mutation the prevalence was lower than that in the general population and for the C282Y mutation in people with haemochromatosis. Some 0.87%[38] to 1.2%[13] of people with haemochromatosis had the H63D homozygous mutation and 0% had the heterozygous mutation.[38] As only two studies assessed the prevalence of the H63D mutation, some caution should be taken in interpreting these results. Similarly, only two studies examined the prevalence of the compound heterozygous mutation (C282Y/H63D) in the haemochromatosis population; one reported a rate of 2.6%,[38] which is similar to the frequency in the general population, and the other, which did not genotype the whole sample, reported a rate of 7.4%.[13] The wild-type genotype was evident in 4.4% of people with haemochromatosis.[38]

Penetrance of the gene mutation

As discussed in the section on description of the health problem, people with the genetic mutation for haemochromatosis may or may not develop the phenotypic condition. Studies assessing the penetrance of the gene mutation within the UK and Ireland were limited. Only McCune and colleagues[13] provided a rate for the penetrance of the gene mutation, identifying a penetrance of 1.2% in the general population.

Prevalence of haemochromatosis

No studies were identified that presented the prevalence of haemochromatosis in the general population in the UK. Merryweather-Clarke and colleagues[67] reported a population prevalence for haemochromatosis of 1 in 4700 in Jersey. Other studies have presented prevalence rates for specific groups who have presented with different signs and symptoms characteristic of increased iron. Emery and colleagues[68] found that 4.2% of people presenting with signs and symptoms of increased iron or who had undergone iron studies and then underwent liver biopsy had confirmed haemochromatosis. Given that this group was a cohort with an increased likelihood of having the condition, it is not surprising that the rate

was considerably higher than that identified by Merryweather-Clarke and colleagues[67] and hence it should be used with caution.

Current service provision

Patients with haemochromatosis are diagnosed, treated and managed by a variety of clinical specialists, mostly in secondary care, including gastroenterologists, haematologists and hepatologists. This may lead to fragmented care, which means that it is difficult to establish standard clinical pathways. It is suggested that the diagnosis should be considered in patients presenting with the early features of haemochromatosis: unexplained weakness or fatigue, abnormal liver function tests, arthralgia/arthritis, impotence, late-onset diabetes, cardiomyopathy and raised ferritin.[52,69,70] Assessment of iron status, particularly TS and SF, can be followed by genotyping. Unpublished data from the UK Haemochromatosis Society suggests that the majority of their members with a diagnosis of haemochromatosis (70%) are identified as a result of being investigated for symptoms related to iron overload such as joint pain and liver disease. Approximately 20% are identified as a result of having an affected family member. Some patients are found incidentally as SF may be performed as part of the investigation of a diverse range of medical conditions (e.g. possible anaemia). There also appears to be a delay of some years between reporting of the first symptom and diagnosis (an average of 9 years in men and 12 years in women). An analysis of hospital admission data for England for the years 2000–3 suggests that 14% of patients at their first episode of care for haemochromatosis also had a diagnosis of liver disease.[71] This supports anecdotal data that patients are still presenting with preventable complications of this treatable disease. The non-specific nature of early symptoms makes diagnosis difficult and, in the absence of screening programmes, diagnosis depends on clinical awareness in the relevant specialties.

In many centres haemochromatosis is often managed by a dedicated team consisting of a clinician supported by a nurse specialist and possibly junior medical staff who will do most of the phlebotomy and provide a day-to-day contact point for the patients. Haematologists, gastroenterologists and hepatologists provide the medical input, with care pathways following the BSH guidelines.[69] Genetic advice may also be provided by the same teams, with some having in-house genotyping services and others using regional centres. Regional genetics centres also provide a service offering advice and family investigation, with referral of patients to the local haematologist/gastroenterologist for phlebotomy and clinical assessment.

Aspects of the diagnosis of haemochromatosis considered in this assessment

The discovery of the gene for haemochromatosis has modified diagnostic and screening approaches to identifying cases that would benefit from treatment. However, there is no consensus as to which factors define a case. Most testing strategies include a combination of biochemical and genetic tests and liver biopsy together with modifying information such as age and gender.[52,72] The most appropriate diagnostic strategy is not clear.

Biochemical testing and liver biopsy

Before the discovery of the common gene mutations, diagnosis of haemochromatosis was based on clinical suspicion including persistently raised TS with no other explanation followed by liver biopsy. Both the BSH[69] and the US College of American Pathologists[35] recommend the TS test as the initial diagnostic test for HHC. This test should be carried out on a fasting sample. Elevated fasting TS indicates iron accumulation and, if this has been demonstrated, the BSH guidelines recommend that the SF concentration is measured. SF concentrations are not usually abnormal in the early stages of iron accumulation but once liver iron concentrations are elevated they rise disproportionately with the degree of liver damage. Liver biopsy with assessment of iron deposition, although previously considered to be the gold standard for diagnosis, is no longer used as a diagnostic tool; however, it is still widely used to confirm cirrhosis and as the only way of determining fibrosis. It is worth noting that biochemical tests are unable to discriminate between different possible causes of iron overload, so although iron overload may suggest a diagnosis of HHC other possible diagnoses will need to be ruled out.

Genetic testing

DNA-based testing can identify people who are homozygous for mutations in the *HFE* gene before symptoms of iron overload become apparent. Although this test identifies people at

risk of developing the symptoms of iron overload, because of the low penetrance of the disorder, only a proportion will go on to exhibit the HHC phenotype. This means that both the sensitivity for detecting phenotypic HHC and the PPV of genetic testing are low in the general population.

A wide range of DNA-based tests to identify the C282Y and H63D mutations have been described, most commonly polymerase chain reaction (PCR) followed by restriction enzyme digest, amplification refractory mutation system PCR, and PCR with single-strand conformation polymorphism (SSCP) analysis.[73]

Family screening

Hereditary haemochromatosis is an autosomal recessive condition and, as such, children and siblings are at increased risk for inheriting susceptibility to the disease, with probabilities of at least 1 in 20 and at least 1 in 4 respectively. The purpose of testing family members is to detect those individuals at risk who would benefit from treatment, and to detect those at risk who do not currently require treatment but who will be monitored for a suitable period of time until the need for future treatment can be ascertained. Testing can also identify those not at risk who can be excluded from further investigations and reassured. Penetrance may be higher in families as they share other genetic and environmental factors, although the main risk factor appears to be possession of the at-risk genotype.[13]

Psychosocial aspects of genetic testing

Concern about genetic testing and screening is evidenced by a number of reports that focus on issues of potential stigmatisation, discrimination, family implications and the possible psychological consequences.[74,75] However, the rationale for genetic exceptionalism may not be well established.[76] In addition, concerns relating to unfair discrimination will be influenced by the legal framework and welfare provision of the country of residence. For example, the situation regarding coverage and reimbursement for health care is very different in North America to that in the UK. In haemochromatosis the purpose of using the genetic test is to identify individuals who will benefit from treatment and to rule out disease in family members. Studies have investigated the psychosocial consequences of using DNA tests for population and targeted screening for haemochromatosis and found few adverse effects.[77–79]

Rationale for this study

There is broad agreement that early diagnosis of haemochromatosis and treatment with venesection is effective at reducing the risk of complications.[1,19] It is important therefore to identify (1) the best diagnostic strategy for those suspected of having haemochromatosis and (2) the best testing strategy for family members to identify those who need treatment or monitoring and those not at risk of haemochromatosis. Biochemical tests will identify the presence of raised iron levels requiring treatment but do not confirm a diagnosis of HHC and diagnostic thresholds are still debated. The additional value of a DNA test is unclear.

From the perspective of the patients and their families the pressing clinical issues are to effectively and efficiently diagnose people early enough so that they may benefit from treatment and to rule out HHC in family members. The wider NHS perspective is to make the most efficient and cost-effective use of the tests available.

Chapter 2

Aim and objectives

Overall aim and objectives of assessment

The aim of this project is to evaluate the use of DNA tests for detecting HHC in subgroups of patients suspected of having the disorder on the basis of clinical presentation and disturbed iron parameters, and in family members of those diagnosed with haemochromatosis. A clear distinction will be drawn between diagnostic strategies in those suspected of having haemochromatosis and testing strategies in family members, as the consequences are different.

The objectives are:

- to determine the clinical validity of DNA tests to diagnose HHC
- to summarise the evidence on the clinical utility of diagnostic strategies using DNA tests to detect cases for treatment or monitoring in terms of clinical effectiveness and cost-effectiveness
- to compare the costs and consequences by decision-analysis modelling of diagnostic algorithms for HHC and family testing strategies with and without DNA testing in terms of cost per case detected
- to review the psychosocial literature and compare the psychosocial benefits and harms of adding DNA testing to diagnostic algorithms
- to identify priorities for future primary research.

Chapter 3
Methods for systematic review

The a priori methods used for the review are outlined in the research protocol (Appendix 1). This was sent to members of the advisory group for the review for expert comments (see Acknowledgements). Helpful comments were received relating to the general content of the research protocol; no specific problems with the proposed methods of the review were identified.

The research methods for the systematic review are summarised in the following sections. The search strategy and inclusion and data extraction process also apply to the systematic searches used to identify information for the economic evaluation (see Appendix 1, *Table 28*, for details of systematic searches on epidemiology, biochemical tests and liver biopsy). Some points of clarification regarding the methods adopted are discussed later in this chapter (see Clarification of methods).

Search strategy

The following databases were searched for published studies and ongoing research, from inception to April 2007: the Cochrane Library (Database of Systematic Reviews and Controlled Trials Register), MEDLINE (Ovid), EMBASE (Ovid), PubMed, Science Citation Index (SCI), BIOSIS, PsychLit, MEDION, NHS Economic Evaluations Database (NHS EED), NHS Health Technology Assessment database (NHS HTA), NHS Database of Abstracts of Reviews of Effectiveness (NHS DARE), EconLit, NRR (National Research Register), Current Controlled Trials and ClinicalTrials. Grey literature and conference proceedings were also searched. Searches were restricted to the English language and to human studies, and for literature on DNA tests for C282Y mutations to 1996 onwards. Bibliographies of related papers were assessed for relevant studies. Investigators of studies were not contacted because of time constraints. Further details, including key search terms, can be found in Appendix 2.

Inclusion and data extraction process

Titles and abstracts of studies identified by the search strategy were screened independently for inclusion by two reviewers. The full text of potentially eligible studies was obtained and examined independently for inclusion by two reviewers. Data were extracted by two reviewers on standard data extraction forms. Any disagreements were resolved by consensus or arbitration by a third reviewer if necessary.

The process for identifying and including studies is illustrated in *Figure 1*. The primary reason for excluding studies was that they did not meet the inclusion criteria. For clinical validity and utility this was because they concerned population or targeted screening, analytical validity, non-European populations, phenotype/genotype correlations or subgroups (such as diabetics or the elderly). A list of studies excluded at various stages of the process can be found in Appendix 3. Ongoing research is shown in Appendix 4.

Quality assessment

The methodological quality of included studies was assessed using modified formal tools specific to the design of the study and focusing on possible sources of bias, which is discussed in the relevant sections throughout the report. Clinical validity studies were assessed using relevant questions from QUADAS (Quality Assessment of Diagnostic Accuracy Studies, Appendix 5)[80] combined with relevant questions from criteria developed by Spitzer and colleagues[81] Aspects considered for quality assessment included adequate description of haemochromatosis patients; appropriate definition of the disease; representative sampling of patients; adequately described control group; whether groups were comparable; description of the tests used and outcomes fully reported; whether

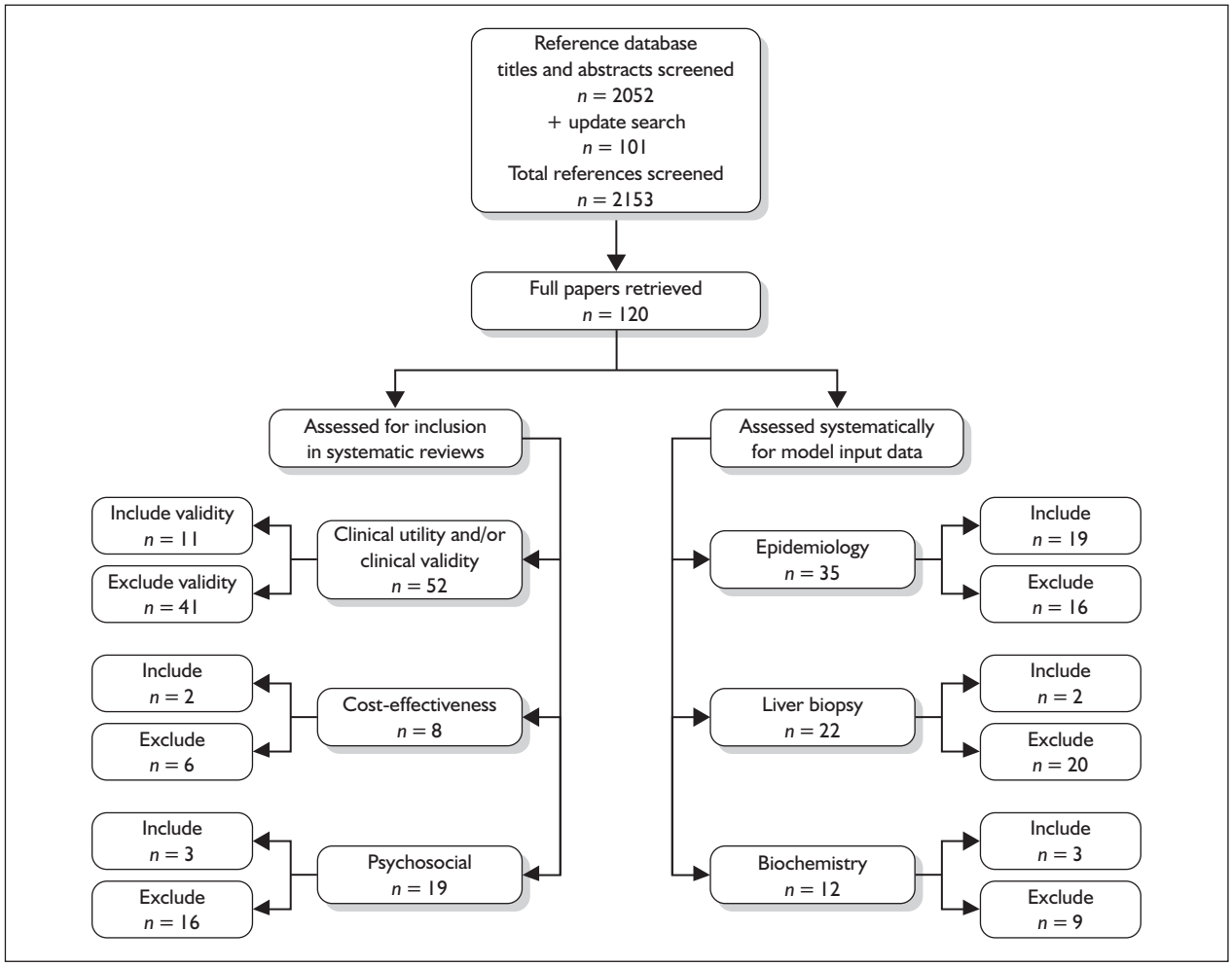

FIGURE 1 *Flow chart of identification of studies for the systematic reviews and searches.*

there were missing data; and generalisability of results. Other observational studies were assessed for quality using the criteria developed by Spitzer and colleagues[81] (Appendix 6). Quality assessment of economic evaluations was conducted using a checklist adapted from those developed by Drummond and Jefferson[82] and Philips and colleagues.[83]

Quality criteria were applied by two reviewers. At each stage, any differences in opinion were resolved through discussion or if necessary by arbitration by a third reviewer.

Inclusion criteria

Inclusion criteria for studies on clinical validity, clinical utility and psychosocial aspects of DNA testing are shown below.

Clinical validity

- Intervention: DNA tests.
- Population: Caucasians with iron overload suggestive of haemochromatosis (north European populations).
- Comparator: control population (Caucasian).
- Outcomes: sensitivity and specificity (reported or calculable).
- Study type: controlled cohort or case–control.

Clinical utility

Clinical effectiveness of diagnostic strategies

- Intervention: DNA tests.
- Population: Caucasians with iron overload suggestive of haemochromatosis; relatives of suspected cases.
- Comparator: any case identification strategy not involving DNA testing.

- Outcomes: treatment, morbidity, mortality, quality of life, psychosocial aspects.
- Study type: RCTs, cohorts with controls, case–control (highest level only).

Cost-effectiveness of diagnostic strategies

- Intervention: DNA tests.
- Population: Caucasian, clinical suspects, defined; relatives of suspected cases.
- Comparator: any case identification strategy, e.g. liver biopsy, phlebotomy or other iron studies.
- Outcomes: cost-effectiveness/utility, costs.
- Study type: economic evaluations, modelling studies.

Psychosocial aspects of DNA testing

- Intervention: DNA tests.
- Population: diagnosed and at-risk individuals (people with suspected HHC and first-degree relatives).
- Outcomes: psychosocial aspects (treatment compliance, psychological outcomes, legal implications, quality of life, discrimination/stigmatisation).
- Study type: any quantitative or qualitative primary research.

Data synthesis

Synthesis of data was through narrative review with full tabulation of results of all included studies. Full data extraction forms are shown in Appendices 7, 8 and 9. Meta-analysis was not possible because of the heterogeneous nature of the studies identified.

Clarification of methods

Some changes, additions or points of clarification were made to the methods discussed in the original protocol. These are presented below:

- There is a large literature relating to haemochromatosis, mostly concerning population screening and epidemiology. Therefore, to identify the most relevant studies and to exclude population screening studies, different inclusion criteria were developed for the different systematic review elements.
- Various authors have raised issues concerning the methods for assessing diagnostic tests and there is a consensus that explicit frameworks should be developed analogous to those used in studies of clinical effectiveness.[84,85] The ACCE model has been developed by the Office of Genomics and Disease Prevention (Center for Disease Control, Atlanta, USA), working with the Foundation for Blood Research to evaluate DNA-based genetic tests,[53] based on original methodology by Wald and Cuckle.[86] This model takes its name from the four components of the evaluation: *A*nalytic validity, *C*linical validity, *C*linical utility and associated *E*thical, legal and social issues. Although still at the development stage it provides a useful framework to inform the evaluation of genetic tests and was the methodology adopted for this review (see also Chapter 8, Other relevant factors, and Appendix 1).
- Analytical validity is the ability of the test to accurately and reliably measure the genotype of interest. It is concerned with assessing test performance in the laboratory and is closely related to quality assurance of the laboratory processes surrounding the test. This is outside the remit of this report.
- Clinical validity refers to the accuracy with which a test predicts the presence or absence of a clinical condition. This involves establishing the probability that the test will be positive in people with the disease (clinical sensitivity) and the probability that the test will be negative in people without the disease (clinical specificity). Clinical sensitivity here refers to the proportion of individuals who have, or who may be destined to develop, the primary iron overload phenotype and who have a positive test result for C282Y homozygosity.
- Traditional diagnostic test assessment is difficult in the case of genetic testing and no studies conforming to the usual format for evaluating clinical validity are available for genetic testing for haemochromatosis. As such, a pragmatic approach was taken to assess clinical validity, which is discussed in more detail in Chapter 8 (Other relevant factors).
- Studies for assessing clinical validity were limited to those involving north European Caucasian populations as these were deemed most relevant to the UK.
- Clinical utility is defined as the likelihood that the test will lead to an improved outcome, and incorporates assessment of the risk and benefits of genetic testing, as well as economic evaluation. This is perhaps the most important aspect of the evaluation in that it assesses whether testing will alter clinical management or benefit those tested and at what cost.

For assessing the clinical utility (i.e. clinical effectiveness and cost-effectiveness) of DNA testing, studies had to compare a strategy incorporating DNA tests with a strategy that did not in people suspected of having haemochromatosis or relatives of patients with haemochromatosis. For clinical effectiveness, studies had to report patient-based outcomes and, for cost-effectiveness, studies had to report some measure of cost and benefit.

- The last component of the ACCE framework was covered by considering psychosocial aspects of using genetic testing for haemochromatosis in terms of psychological issues, quality of life and discrimination and stigmatisation implications. For the psychosocial review, any study type in diagnosed and at-risk populations reporting primary data on psychosocial outcomes of the use of DNA tests in haemochromatosis was included.

Chapter 4

Assessment of clinical validity

Quantity and quality of research available

Eleven controlled cohort studies[38,62,87–95] met the inclusion criteria for the review of clinical validity and are shown in *Table 3* and Appendix 7. Two studies were conducted in the UK,[38,95] two in Ireland,[63,93] three in France,[90,91,94] two in Sweden,[87,89] and two in Germany.[88,92]

Details of the participants in both haemochromatosis and control cohorts, the methodology used to genotype participants, the reported outcomes, the comparability of groups and the generalisability of the studies are presented in the following sections. *Table 4* reports the quality assessment of the included studies.

Haemochromatosis cohorts

Eight of the 11 included studies reported clear selection criteria for the eligibility of haemochromatosis cases[38,87–90,92,94,95] whereas the three remaining studies were unclear and did not report sufficient details.[62,91,93] The criteria used to define haemochromatosis cases varied between studies but most required the presence of two or more diagnostic criteria. Six studies[38,87,88,90,92,95] have used a definition that is likely to correctly classify HHC whereas the remainder are unclear from the description given.

Seven studies[87–89,91–94] included a requirement for both a high TS and a high SF concentration in their haemochromatosis patient definition. Five studies[87–89,92,94] defined an elevated TS and this ranged from a cut-off of over 45% to a cut-off of over 62%. These five studies also defined an elevated SF and this ranged from a cut-off of over 200 µg/l (women only) to a cut-off of over 400 µg/l (men only). Two[91,93] of the seven studies did not state what values of TS or SF would be considered high. One additional study[95] used a high TS concentration (greater than 60%) without mention of SF levels. Three studies did not use TS and SF values.[38,62,90]

In six studies[62,87,88,90,92,93] all members of the haemochromatosis cohort had results from liver biopsy that showed liver iron deposition, and four studies reported that haemochromatosis cohort members had a hepatic iron index (HII) greater than 1.9[38,88] or greater than 2.[90,95] One study[92] used a value of iron from wet weight of liver and reported that haemochromatosis cohort members had an HII of over 30. Phlebotomy treatment for either some or all of the haemochromatosis cohort was a feature of seven studies.[38,87–90,92,95] Only four studies[38,87,88,90] reported that other causes of iron overload had been ruled out. One study[62] provided few details about the diagnosis of the patients in the haemochromatosis cohort, reporting only that 'haemochromatosis cases were both clinically assessed and pathologically diagnosed by liver biopsy'.

In all studies it is not clear whether bias has been avoided in the sampling of participants in the haemochromatosis cohorts as the methods used have not been described. Most of the haemochromatosis patient cohorts comprised fewer than 100 individuals[62,87,88,92,93,95] (range 18–92), three cohorts comprised 115–156 individuals,[38,90,94] there was one patient cohort of 296[89] and the largest contained 478 haemochromatosis patients.[91] Individuals in five of the haemochromatosis cohorts[38,87,88,90,92] were reported to be unrelated to one another, and in one study[93] although the majority of the cohort consisted of unrelated individuals it is not clear whether this is true for the entire cohort. One haemochromatosis cohort is reported to include some related individuals.[95] Only three studies[88,91,95] specifically state that the patients are Caucasian, with a further study cohort[94] being predominantly Caucasian (96.2%).

Only two studies[92,94] report some additional characteristics for their haemochromatosis cohort, and three studies[87–89] report on the age and sex of the cohort.

Control cohorts

Control subjects were drawn from different sources in the included studies and may not be representative of the population that the haemochromatosis patients were drawn from and may not be free from selection bias. In four studies[87,90,91,94] the control cohort was drawn

TABLE 3 *Studies used to assess clinical validity*

Study details	Haemochromatosis cohort	Control cohort
Cardoso *et al*. 1998;[87] Sweden	Unrelated patients with high TS (> 60% in men and > 50% in women) and SF > 300 μg/l and LB with typical iron staining indicating primary HHC (*n* = 87)	Random healthy Swedish subjects (*n* = 117)
Hellerbrand *et al*. 2001;[88] Germany	Unrelated patients diagnosed on basis of clinical history and meeting following criteria: (1) increased TS (repeatedly > 50%) and elevated SF levels; (2) hepatocellular hemosiderin deposits of grade III–IV; (3) HII > 1.9 and/or total iron removed > 5g (men) and > 3g (women) (*n* = 36)	Healthy hospital employees (*n* = 126)
Holmstrom *et al*. 2002;[89] Sweden	SF > 300 μg/l (men) or > 200 μg/l (women) or TS > 50% (men) or > 45% (women) (*n* = 296)	Hospital staff and students and their relatives (no history of liver disease or multiple blood transfusions) (*n* = 250)
Jouanolle *et al*. 1997;[90] France	Unrelated participants diagnosed on basis of clinical and biological signs with at least one of increased stainable iron in at least 75% of hepatocytes; hepatic iron concentration > 100 μmol/g dry weight; HII > 2; more than 5 g of iron removed by weekly phlebotomy (*n* = 132)	Random subjects from general population (not defined) (*n* = 139)
Mura *et al*. 2005;[91] France	Diagnosis based on classic signs and symptoms: elevated TS and/or SF concentration; hepatic symptoms, such as unexplained elevation of serum liver enzymes, cirrhosis, liver failure, or diabetes mellitus; and non-specific compatible symptoms, e.g. fatigue, abdominal pain, joint pain, cardiac arrhythmia and hyperpigmentation (*n* = 478)	Randomly selected, Caucasian (*n* = 410)
Murphy *et al*. 1998;[62] Ireland	Clinically assessed and pathologically diagnosed by LB (*n* = 30)	Normal volunteers (bone marrow registry) (*n* = 404)
Nielsen *et al*. 1998;[92] Germany	Unrelated patients diagnosed by the presence of at least three of the following criteria: (1) TS > 62%; SF > 300 μg/l; (2) LIC > 2000 μg Fe/g wet weight; (3) HII [HI (μg/year) = (LIC/age)] > 30; (4) grade III or IV stainable iron in liver; (5) > 4 g of iron removed by phlebotomy (*n* = 92)	Unrelated healthy volunteers of German ancestry (*n* = 157)
Ryan *et al*. 1998;[93] Ireland	Patients diagnosed on basis of clinical history, physical examination, persistently raised TS and SF and, for group 1, > 3+ hepatic iron deposition (*n* = 60) and, for group 2, < 3+ iron deposition on liver biopsy (*n* = 18)	Randomly selected individuals from hospital staff (not defined) (*n* = 109)
UK HHC Consortium 1997;[38] UK	Unrelated patients with, in the absence of any other cause of iron loading, either HII > 1.9 or > 5 g mobilisable iron by quantitative phlebotomy (*n* = 115)	Series of unrelated healthy blood donors (*n* = 101)
Vantyghem *et al*. 2006;[94] France	General symptoms (fatigue, weight loss, arthralgia), diabetes, hepatomegaly, disturbed liver enzymes or hypogonadism and abnormal iron markers (SF > 300 ng/ml or TS > 45%) (*n* = 156)	Healthy Caucasian subjects without family history of diabetes or iron overload (*n* = 106)
Willis *et al*. 1997;[95] UK	Patients being treated for HHC by phlebotomy. Criteria: fasting TS > 60% in two samples and HII > 2 where appropriate (*n* = 18)	Referred to hospital for reasons unrelated to known manifestations of HHC and representative of hospital population (different patient groups included) (*n* = 200)

HI, hepatic iron; HII, hepatic iron index; LB, liver biopsy; LIC, liver iron content; SF, serum ferritin; TS, transferrin saturation.

from the general population; only two of these studies[91,94] clearly state that the control group subjects are Caucasian. Three studies recruited the control cohort from amongst hospital employees[88,93] or hospital employees and students and their relatives.[89] Three studies[38,62,92] recruited from particular groups of healthy persons, including blood donors[38] and a bone marrow registry.[62] The remaining study recruited the control cohort from amongst several other patient groups.[95]

Sampling of the control cohorts was described as random in four studies,[87,90,91,93] with the sampling methods being unclear in five studies;[38,88,89,94,95] the remaining studies involved volunteers.[62,92]

DOI: 10.3310/hta13230

TABLE 4 *Quality assessment of clinical validity studies*

Item	Cardoso *et al.* 1988[87]	Hellerbrand *et al.* 2001[88]	Holmstrom *et al.* 2002[89]	Jouanolle *et al.* 1997[90]	Mura *et al.* 2005[91]	Murphy *et al.* 1998[62]	Nielsen *et al.* 1998[92]	Ryan *et al.* 1998[93]	UK HHC 1997[38]	Vantyghem *et al.* 2006[94]	Willis *et al.* 1997[95]
1. Were selection criteria for eligibility of patients objective and clearly described to allow replication?	Y	Y	Y	Y	U	U	Y	U	Y	Y	Y
2. Is the definition of iron overload likely to correctly classify HHC?	Y	Y	U	Y	U	U	Y	U	Y	U	Y
3. Did the study use proper sampling so that all patients were equally likely to enter the study?	U	U	U	U	U	U	U	U	U	U	U
4. Was the control population appropriate?	U	N	N	N	Y	N	N	N	U	Y	N
5. Did the study use proper sampling so that all control subjects were equally likely to enter the study?	Y	U	U	Y	Y	N	N	Y	U	U	U
6. Was the DNA test method described in sufficient detail to permit replication?	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
7. Was the execution of biochemical methods described in sufficient detail to permit replication?	N	N	U	n/a	N	n/a	N	N	N	U	n/a
8. Were groups under comparison comparable in terms of age, sex and race?	U	U	N	U	U	U	U	U	U	U	U
9. Was there any mention of missing data?	N	N	Y	N	N	N	N	N	N	N	N
10. Was the sample of patients representative of the patients who will receive the test in practice, i.e. are results generalisable?	Y	Y	U	Y	U	U	Y	U	Y	U	Y

Y, yes; N, no; U, unclear; n/a, not applicable (no biochemistry results given).

All of the control cohorts comprised more than 100 individuals. One cohort comprised 200 individuals,[95] one 250 individuals,[89] and the two largest control cohorts contained 404[62] and 410[91] subjects. Only two studies[38,92] reported that the individuals in the control cohort were unrelated to one another, and in one study[89] the inclusion criteria allowed for related individuals to be included.

Only one study[92] reported some additional characteristics for the control cohort, and one study[89] reported age and sex of the cohort, noting that these parameters were significantly different from those of the haemochromatosis cohort.

Genotyping methodology

To analyse the *HFE* gene regions encompassing the C282Y and H63D mutation sites eight studies[38,87,88,90–94] isolated genomic DNA and performed a PCR followed by restriction enzyme digest of the PCR products [restriction fragment length polymorphism (RFLP) analysis] to determine whether samples carried the two mutations of interest. One study[95] used this method only for H63D mutation determination. The primers used for the PCR varied between studies. Six studies[38,87,88,90–92] published the sequences of some or all of the primers used, two studies[93,95] cited a reference and one study[94] provided no information at all about the PCR primers used. To identify wild-type and mutant C282Y PCR products by RFLP the restriction enzymes Rsa1[38,90,93,94] or SnaB1[87,88,91,92] were used, and for H63D the restriction enzymes Bcl1[38,87,88,91,92,94,95] or Mbo1[90,93] were used. Only two of the studies[38,93] using the PCR-RFLP method specifically mention that primers had been modified to include an internal control restriction site. One study[90] had analysed the C282Y and H63D loci in DNA samples from haemochromatosis and control cohorts by fluorescent sequencing before conducting the PCR-RFLP analysis. Another study,[88] in addition to the PCR-RFLP analysis, also performed a PCR-ELISA (enzyme-linked immunosorbent assay) to analyse the C282Y mutation, and a single-strand conformation polymorphism analysis for capillary electrophoresis (SSCP-CE) analysis for both C282Y and H63D mutations in the *HFE* gene.

Two studies performed a PCR and then immobilised the PCR products on membranes so that hybridisation with normal and mutant versions of C282Y[62,95] and H63D[62] could be carried out to identify whether samples carried the mutations of interest. One study[62] published the sequences of the primers used for the PCR and the other study[95] cited a reference. Both studies published the sequences of the probes used in the hybridisation. One study[62] also stated that a number of the PCR products had been sequenced to confirm that the correct region of the *HFE* gene had been amplified, and samples of known genotype were also included as a control in the hybridisations.

In the 10 studies described above samples from the haemochromatosis cohort and the control cohort were analysed in the same way. In one study[89] different methods were used for the two cohorts. DNA samples from the haemochromatosis cohort were sequenced to identify the mutations of interest; details of the primers used in the sequencing reaction are not provided. DNA samples from the control cohort were analysed by PCR-RFLP (references are cited for this method) and all substitutions detected by RFLP were confirmed. For C282Y the RFLP was repeated, and for H63D samples were sequenced to confirm the result.

Outcomes

All studies reported on the prevalence of the *HFE* mutations C282Y and H63D in the haemochromatosis and control cohorts. Two studies[89,91] also reported on the *HFE* mutation S65C. Other commonly reported outcomes included allele frequencies in haemochromatosis[87,91,94] and/or control cohorts,[62,87,91,94,95] clinical data for haemochromatosis patients who were not C282Y homozygous,[38,87,88,93] genotype–phenotype correlations for the haemochromatosis cohort[89,94] or both cohorts,[92] and haplotype analysis.[38,90]

Withdrawals and dropouts were not applicable to these studies but one study reported missing SF and TS data for the haemochromatosis group.[89]

Comparability of groups

In one study[89] the haemochromatosis and control groups are not comparable in terms of age, sex and race/ethnicity and in all other studies it is not clear whether the groups are comparable.

Generalisability

The results of six studies[38,87,88,90,92,95] may be generalisable in terms of them being from representative samples of unrelated Caucasian haemochromatosis patients. It is unclear whether the results of the other studies are generalisable.

Results of the clinical validity studies

Estimates from the included studies of the clinical sensitivity, clinical specificity, PPV and negative predictive value (NPV) of the genetic mutation C282Y for the iron overload phenotype in northern European Caucasians are summarised in *Table 5*.

Sensitivity

Clinical sensitivity ranges from 28.4% to 100% as determined from the included studies. The definitions of primary iron overload are variable, which may account for the wide range. When considering only the studies that are most likely to correctly define haemochromatosis,[38,87,88,90,92,93,95] clinical sensitivity ranges from 72.2% to 100%. If the studies are further limited to those that have reported that other causes of iron overload have been ruled out and that patients are unrelated, the range is 72.2–92.4%.[38,87,88,90] The range is 91.3–92.4% when the small study in southern Germany, which may be on the north–south European divide, is excluded.[88]

From two studies the estimated clinical sensitivity is low at 28.4%[89] and 21.1%.[94] This may be explained in one study[89] by the fact that *HFE* testing was carried out retrospectively in patients with clinical suspicion of iron overload based only on biochemical measurements, some of which were missing. The other study with low clinical sensitivity included patients referred to a hospital endocrinology and metabolism department with excessive alcohol intake and diabetes, in whom disturbed iron parameters may have been due to cirrhosis and insulin resistance, respectively, and not to genetic iron overload.[94]

Clinical sensitivity was 100% in one small study of 18 patients, which included related subjects.[95]

Specificity

Clinical specificity ranges from 98.8% to 100% from the included studies. In two[38,89] of the five studies that give an estimate below 100%, the single individual homozygous for the C282Y mutation in the control group showed signs of evidence of iron overload. No details are given about the homozygous individuals in the control

TABLE 5 *Clinical sensitivity, clinical specificity, positive predictive value (PPV) and negative predictive value (NPV) of DNA testing*

Study[a]	Country	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Cardoso *et al.* 1998[87] (*n* = 87/117)	Sweden	92	100	100	94.4
Hellerbrand *et al.* 2001[88] (*n* = 36/126)	Germany	72.2	100	100	92.7
Holmstrom *et al.* 2002[89] (*n* = 296/250)	Sweden	28.4	99.6	98.8	54
Jouanolle *et al.* 1997[90] (*n* = 132/139)	France	92.4	100	100	93.3
Mura *et al.* 2005[91] (*n* = 478/410)	France	81.2	99.5	99.5	81.9
Murphy *et al.* 1998[62] (*n* = 30/404)	Ireland	90	98.8	84.4	99.3
Nielsen *et al.* 1998[92] (*n* = 92/157)	Germany	94.6	100	100	96.9
Ryan *et al.* 1998[93] (*n* = 18/109)	Ireland	93.3	100	100	96.5
UK HHC Consortium 1997[38] (*n* = 115/101)	UK	91.3	99	99	91
Vantyghem *et al.* 2006[94] (*n* = 156/106)	France	21.2	100	100	46.3
Willis *et al.* 1997[95] (*n* = 18/200)	UK	100	99.5	94.7	100

a *n* = number in haemochromatosis group/number in control group.

groups of the other three studies[62,91,95] so it is not known if they showed signs of irregular iron loading or whether they would in the future. However, specificity may be less than 100% as some homozygotes in the control group may never exhibit symptoms.

Positive predictive value and negative predictive value

The PPV ranges from 84.3% to 100% and the NPV from 46.3% to 100%. As expected these values reflect those of the clinical specificity and clinical sensitivity, respectively, and show a range of values for the reasons given above. Considering the most appropriate studies the PPV ranges from 99% to 100% and the NPV from 91% to 94.4%.

Summary of clinical validity

- Eleven studies were identified that could be used to estimate the clinical validity of genotyping for the C282Y mutation for the diagnosis of genetic haemochromatosis.
- The quality of the studies using the criteria developed for this review is variable.
- The studies used a range of definitions for the clinical phenotype. Six of the studies used criteria likely to correctly classify HHC, the results of which are likely to be generalisable.
- The clinical sensitivity of C282Y homozygosity for HHC ranged from 28.4% to 100% in the 11 studies. When using only the six studies most likely to have correctly defined haemochromatosis, sensitivity ranged from 72.2% to 100%. By further limiting the studies to those that have reported ruling out other causes of iron overload and related patients, the range is 72.2–92.4%. The range is 91.3–92.4% when only the most northerly populations are included.
- When strict inclusion criteria for phenotypic expression are used in relevant populations the clinical sensitivity increases.
- Clinical specificity ranged from 98.8% to 100%.

Chapter 5
Clinical utility

No clinical effectiveness studies meeting the inclusion criteria for the review were identified. Two cost-effectiveness studies were identified and are reported in Chapter 7 (Systematic review of the literature).

Chapter 6

Psychosocial aspects of DNA testing

DNA-based testing for mutations in the *HFE* gene can be conducted to confirm a diagnosis of HHC in those who already have clinically apparent symptoms of iron overload. The DNA test can also identify people who may be at risk of developing iron overload enabling them to benefit from early treatment. However, the low penetrance of this disorder means that only a proportion of those identified as 'at risk' will progress to exhibit the HHC phenotype. In common with other predictive tests (including non-genetic tests) the potential harms of testing must also be taken into account. Concerns have been raised among academics, policy-makers, the media and the public that genetic testing may lead to stigmatisation, discrimination, family conflict and psychological harm.

In this section of the report the literature on the psychosocial aspects of DNA testing for haemochromatosis in diagnosed and at-risk individuals (people with suspected HHC and their first-degree relatives) is reviewed to assess the psychosocial benefits and harms of adding DNA testing to the existing diagnostic algorithms.

Quantity and quality of research available

Three cohort studies met the inclusion criteria for the review. One study was a cohort study with a control group,[96] one cohort study compared clinically affected with clinically unaffected patients[97] and one study compared patients according to genotype for one outcome.[98] The methodological quality of the included studies was assessed using the criteria developed by Spitzer and colleagues.[81] None of the studies was carried out in the UK. A summary of the studies is shown in *Table 6* and the quality assessment of the studies is shown in *Table 7*. Full data extractions are given in Appendix 8.

Sampling methods were not clearly reported or discussed in any of the cohort studies so it is not possible to determine whether sampling bias has been avoided. In the report of the controlled cohort study[96] all patients who met the eligibility criteria were invited to take part in the study. However, the time frame over which patients were enrolled is not reported, and it is not clear how many eligible patients there were and what proportion of them agreed to enter the patient cohort. All eligible patients were also invited to participate in one of the uncontrolled cohort studies;[97] patients were enrolled over a 2-year period and all completed the baseline questionnaire. Power and Adams[98] drew their participants from two sources. Most ($n = 117$) were patients referred for diagnostic evaluation for haemochromatosis, but a second group ($n = 25$) were all of those people identified by a population screening study as homozygotes (subsequently nine were found to be heterozygotes). The subgroup of 25 people identified by population screening does not meet the inclusion criteria for our review and so the results for this group have not been reported on except when it has not been possible to separate out these results from those of the referred patient group. The time frame over which the referred patients were enrolled is not given, and again it is not clear whether all of the potentially eligible referred patients took part.

None of the studies reported whether their sample size was likely to be adequate. The control cohort in the only controlled study[96] comprised 50 individuals. Patient cohorts ranged in size from 87 to 142, but two of the studies[97,98] subdivided their patient cohort into smaller groups for some analyses according to genotype[98] or clinical presentation.[97] Only one study[98] acknowledges that the small sample size for some of the outcomes means that there may not have been sufficient power to detect significant differences between the groups.

All of the studies reported on objective outcomes but none of the studies reported on whether blinded assessment was carried out and so it is not possible to determine whether the studies are free from measurement bias. One study[96] did report that two independent raters categorised the answers to short-answer questions using a coding system. Those studies employing the Impact of Event Scale (IES),[97] the Spielberger State–Trait Anxiety Inventory (STAI-State),[97,98] the Short-Form

TABLE 6 *Summary of psychosocial studies*

Study	Design	Outcomes	Intervention details	Age and sex
Hicken *et al*. 2004;[96] USA	Cohort with control	Participation in testing; emotional reactions; understanding and knowledge; perceived effects of testing; compliance with treatment	**HHC cohort (*n* = 87)**: Structured interview for reporting attitudes about genetic testing and understanding of genetics and haemochromatosis; average delay between genotyping and interview was 3 years **Control cohort (*n* = 50)**: The same structured interview as haemochromatosis patients but control subjects estimated the reactions that they would have if they underwent genetic testing	**Age**: HHC cohort 53.9±12.5 years (range 25–82); control cohort 58.5±13.7 years (range 31–80) **Male (%)**: HHC cohort 55%; control cohort 56%
Meiser *et al*. 2005;[97] Australia	Cohort without control	STAI-State; SF-36; Impact of Event Scale; understanding and knowledge	Self-administered questionnaires including standardised measures of psychological and quality of life outcomes (Impact of Event Scale, STAI-State short version and SF-36). Participants assessed just before clinic visit, 2 weeks after clinic visit and 12 months after clinic visit (*n* = 101)	**Mean age:** 45 years (range 18–69) **Male (%)**: 61.6%
Power and Adams 2001;[98] Canada	Cohort without control	STAI-State; Feelings About Test Result Measure	SF-36 and STAI. Participants completed the questionnaires before learning about their test results and immediately after learning of their test results (*n* = 117; outcomes for which results could not be separated include an additional 25 participants recruited from a screening programme)	**Age**: 46±13 years **Male (%)**: not reported

SF-36, Short-Form 36 Health Survey; STAI-State, Spielberger State–Trait Anxiety Inventory.

TABLE 7 *Summary of the quality assessment of the psychosocial outcomes studies*[81]

Criteria	Hicken *et al*. 2004[96]	Meiser *et al*. 2005[97]	Power and Adams 2001[98]
Proper random assignment	n/a	n/a	n/a
Proper sampling	NR	NR	NR
Adequate sample size	87 patients, 50 control subjects	101 (62 at 12 months)	117
Objective outcomes	Y	Y	Y
Blind assessment	NR	NR	NR
Objective eligibility criteria	Y	U	U
Reported attrition	Y	I	NR
Comparability of groups	N	n/a	n/a
Generalisability	U	U	U

Y, yes; N, no; U, uncertain; I, incomplete; NR, not reported; n/a, not applicable.

36 Health Survey (SF-36)[97,98] and the Feelings About Test Result Measure[98] commented that these instruments had been validated or used in similar studies. The validity of the other methods used in the studies to assess other outcomes (several of which used either a 5-point or a 4-point Likert-type scale) was not generally commented on, except in one instance when it was acknowledged that the

measure of knowledge about haemochromatosis had not been validated and therefore its reliability and validity characteristics were unknown.[97]

Eligibility criteria were clearly reported by only one study;[96] they were unclear in the other two studies.[97,98] Where the eligibility criteria are unclear it is difficult to ascertain whether the participants were correctly classified as having, or being at risk of, haemochromatosis. In the cohort study with a control group[96] all participants had to be Caucasians over 18 years of age. Those in the haemochromatosis cohort also had to have haemochromatosis with iron overload, to have undergone phlebotomy to reduce or maintain ferritin levels at the study centre between January 1990 and May 2000, and to have been genotyped at least 1 year before chart review. Those in the control cohort had to report that they did not have haemochromatosis and had not undergone *HFE* genotyping. All of the control subjects were people with hypertension who were enrolled in a hypertension clinical trial. One study[97] reported only exclusion criteria. Patients were ineligible for the study if they were unable to give informed consent or if they had limited literacy in English. It is not stated explicitly whether all other patients were eligible to participate. In the study in which participants were drawn from two sources,[98] the eligibility criteria for the group of participants referred to the haemochromatosis clinic were unclear. Participants had suspicious symptoms, a family history or abnormal iron blood tests, but the exact clinical criteria (e.g. what constituted an abnormal iron blood test result) are not reported.

Hicken and colleagues[96] clearly report participant attrition and the reasons for this. In total, 12% of their patient outcome data (interviews with 10 patients) were pilot data and were included only in the analyses of outcomes and attitudes about genetic testing. In addition, 34% of patients could not recall undergoing *HFE* genotyping and so were not able to contribute data on the psychosocial outcomes of genetic testing. The participants who could not recall undergoing *HFE* genotyping were not significantly different to those who did remember undergoing *HFE* genotyping in terms of age, time since *HFE* genotyping or knowledge about haemochromatosis. The other two studies either have incomplete reporting of participant attrition[97] or do not report or comment on participant attrition at all.[98] All participants in the Meiser and colleagues study[97] are reported as having completed a baseline questionnaire; however, it is apparent from the tables of patient characteristics and the results tables that some baseline data are missing and this is not discussed by the authors. Loss to follow-up at both the 2-week and 12-month post-consultation time points is reported together with an assessment of the differences between participants who were retained and those who were lost to the 12-month follow up. Participants lost at the 12-month follow-up were more likely not to have post-school education ($p = 0.021$) and had significantly worse mental health ($p = 0.031$). Participant attrition is not reported or discussed in the remaining study but it is clear from the results presented that data are not available for all participants.[98] In this study there is doubt about how many participants have contributed to some of the reported outcomes, whereas for other outcomes the number of participants contributing data is clearly stated.

Only one of the cohort studies included a control group.[96] The characteristics of both groups are provided and it is acknowledged that for the characteristics of marital status and health insurance there are significant differences between the groups with more patients being married in the HHC cohort than in the control cohort (82% versus 58%, $p < 0.001$) and more patients having health insurance in the HHC cohort than in the control cohort (98% versus 84%, $p < 0.01$). The studies that did not have a control group subdivided their patient cohort in reporting some outcomes. These studies did not report on the characteristics of their subgroups and whether they were comparable.[97,98]

Generalisability to the UK population being considered in the context of this Health Technology Assessment (HTA) report is difficult to determine for all of the included studies. Eligibility criteria are clearly reported in only one study,[96] although the other two studies[97,98] do provide some details on the characteristics of the participants. One issue not yet discussed, which may also impact on the generalisability of the results, is the timing of data collection in relation to the execution of the genetic test. Only one study assessed all participants before they had been informed of their genetic testing results.[98] However, only the subset of 25 participants (all homozygotes or heterozygotes) was followed up after 1 year and reassessed and these participants do not meet the inclusion criteria for this review and so their results are not reported on here. In the only other study that assessed participants before their attendance at the study centre,[97] genetic testing results were available for only 95 of the 101 participants; however, of these 95 participants, 80 (84.2%) had already learnt of

their genetic testing result before clinic attendance and it is not clear whether they knew of their test result when they completed the baseline (preclinic) assessment. Only 15.8% learnt their genetic testing result when they attended the clinic. This study also followed up participants at the later time points of 2 weeks and 1 year after clinic attendance; however, there was substantial loss to follow-up. The length of time between genotypic testing and interviewing participants is an important issue in the controlled cohort study in which the average delay between *HFE* genotyping and study assessment was 3 years, which may lead to recall bias.[96] In this study participants were not asked about their feelings at the time of the test but they were asked to recall details about the information they received before *HFE* genotyping.

Assessment of psychosocial aspects of DNA testing

Tables 8–12 summarise the psychosocial aspects of DNA testing for haemochromatosis. The outcomes are detailed in the following sections; not every study reported on each of these outcomes.

Participating in testing

Only one study[96] reported outcomes of participating in testing (*Table 8*). Most patients who could recall having the genetic test stated that they were satisfied with the information they had received before the test, had wanted to receive the test and had understood the rationale for being tested. People who could not recall having the genetic test (34%, $n = 30$) did not contribute to this outcome measure.

Emotional reactions

All three studies reported on the emotional reactions experienced by people in response to receiving the *HFE* genetic test (*Table 9*). However, the only common outcome measures among the studies were the STAI and the SF-36, which were both reported by two studies.[97,98]

Spielberger State–Trait Anxiety Inventory

Meiser and colleagues[97] surveyed a sample of 101 patients who attended a haemochromatosis clinic and report the mean STAI-State scores for both clinically unaffected and clinically affected participants (participants were categorised as 'affected' by the study clinician based on published criteria, which included the presence of diabetes, cardiac involvement, endocrine dysfunction, stigmata of the liver and cirrhosis), and the groups combined at three time points: baseline, 2 weeks post consultation and 12 months post consultation. There were no significant differences in the mean STAI-State scores of clinically unaffected and clinically affected individuals at baseline ($p = 0.89$). Similarly there were no significant differences between the clinically unaffected and the clinically affected individuals at the two other time points. In addition, changes across time points were not suggested by the data and Meiser and colleagues state that this was confirmed by statistical analyses although no details are provided. It was noted, however, that the STAI-State scores were high, indicating increased levels of generalised anxiety. Meiser and colleagues report that there were no statistically significant associations between baseline generalised anxiety and age, sex, educational level, marital status or ferritin levels.

Power and Adams[98] used the STAI to assess change in emotional reaction before and after genetic testing. Participants' anxiety scores were recorded before genotyping was carried out and a year after genotyping. As there was no significant difference between the mean STAI scores of the two patient groups the data were pooled for analysis. The combined data are reported here although it should be remembered that this outcome includes data from the 25 participants identified by population screening who do not meet the inclusion criteria of this review. When all participants were considered as one group the

TABLE 8 *Summary of outcomes of participating in testing (n = 57)*

Participating in testing, Hicken et *al*. 2004[96]	Mean ± SD (range)[a]
Satisfaction with information received	3.39±0.59 (2–4)
Wanted to undergo *HFE* genotyping	3.38±0.56 (2–4)
Understood rationale for testing	3.38±0.59 (2–4)

a Agreement rated 1–4 (1 = strongly disagree; 4 = strongly agree).

TABLE 9 *Summary of outcomes of emotional reactions*

STAI-State short version, Meiser *et al*. 2005[97]							
	Unaffected mean (SD)		**Affected mean (SD)**		**Total mean (SD)**		***p*-value**
Baseline	45.8 (7.6), $n = 59$		45.5 (8.6), $n = 26$		45.8 (7.7), $n = 89$		0.89[a]
2 weeks post consultation	44.6 (7.1), $n = 38$		46.5 (7.1), $n = 18$		45.1 (7.0), $n = 58$		0.37[a]
12 months post consultation	43.2 (5.9), $n = 21$		44.6 (5.1), $n = 16$		43.8 (5.6), $n = 37$		0.45[a]
STAI-State, Power and Adams 2001[98]							
	wt ($n = 35$)		**HET ($n = 23$)**		**HOM ($n = 27$)**		
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**	***p*-value**
Pretest and post-test change in mean STAI (values read from chart)	40.4	38.8	37.2	32.2[b]	39.7	34.0[b]	< 0.05[b]
SF-36, Meiser *et al*. 2005[97]							
	Unaffected mean (SD)		**Affected mean (SD)**		**Total mean (SD)**		***p*-value**
PCS at baseline	49.0 (7.7), $n = 59$		42.9 (10.7), $n = 28$		46.9 (9.4), $n = 91$		0.02[a,c]
PCS at 2 weeks post consultation	47.8 (9.4), $n = 42$		43.6 (10.0), $n = 20$		46.4 (9.7), $n = 65$		0.06[a]
PCS at 12 months post consultation	45.1 (11.5), $n = 23$		41.1 (14.0), $n = 17$		43.4 (12.6), $n = 40$		0.50[a]
MCS at baseline	46.7 (9.7), $n = 59$		42.3 (10.5), $n = 28$		45.3 (10.0), $n = 91$		0.06[a]
MCS at 2 weeks post consultation	47.2 (9.8), $n = 42$		42.5 (12.0), $n = 20$		45.6 (10.6), $n = 65$		0.17[a]
MCS at 12 months post consultation	51.0 (8.5), $n = 23$		45.7 (9.6), $n = 17$		48.7 (9.3), $n = 40$		0.08[a]
Emotional reactions summary measures, Hicken *et al*. 2004[96]							
	Control subjects (anticipated), mean rating		**Patients (actual), mean rating**				***p*-value**
Positive outcomes	13.14		12.44				> 0.5
Negative outcomes	17.56		13.39				< 0.0001
Emotional reactions individual negative measures (values from graph), Hicken *et al*. 2004[96]							
	Control subjects (anticipated), mean rating		**Patients (actual), mean rating**				***p*-value**
Anxious	3.1 ± 0.6		1.8 ± 0.8				< 0.0001
Sad	2.4 ± 0.7		1.8 ± 0.6				< 0.0001
Angry	1.9 ± 0.7		1.5 ± 0.6				< 0.005
Cost	2.8 ± 0.8		1.7 ± 0.7				< 0.0001
Family conflict	1.7 ± 0.6		1.6 ± 0.6				
Job or insurance loss	2.0 ± 0.7		1.9 ± 0.8				
Discrimination	2.0 ± 0.6		1.8 ± 0.8				
Confidentiality	2.2 ± 0.8		1.9 ± 0.7				

continued

TABLE 9 *Summary of outcomes of emotional reactions (continued)*

Impact of Event scale, Meiser *et al*. 2005[97]				
	Unaffected mean (SD)	**Affected mean (SD)**	**Total mean (SD)**	***p*-value**
2 weeks post consultation	4.0 (5.8), $n = 44$	5.6 (6.8), $n = 21$	4.6 (6.2), $n = 68$	0.48[a]

wt, wild type; HET, heterozygotes; HOM, homozygotes.
a *p*-value for comparison between clinically affected and unaffected participants.
b *p*-value for comparison with pretest value. These results include data from the 25 participants identified by population screening who do not meet the inclusion criteria of this review.
c Significant at $p < 0.05$.

mean (±SD) STAI state anxiety score significantly decreased from 39.15 (±11.45) before testing to 35.54 (±11.46) after testing ($n = 142$, $p < 0.01$). The authors also analysed these results according to subjects' genotype (results presented in a figure for 85 of the 142 participants; reasons for missing data not given). This analysis showed that it was only in those who discovered that they were homozygotes or heterozygotes that anxiety significantly decreased ($p < 0.05$). Those participants who tested negative for the C282Y mutation had an anxiety level that remained constant before and after the test. None of the mean STAI scores lay outside the normal range of 25–45.

Short-Form 36

Meiser and colleagues[97] used the SF-36 to assess health-related quality of life. For all indices of the SF-36 subscales, clinically unaffected individuals had higher scores (indicating better health or well-being) than affected individuals and these differences were statistically significant for most subscales: role–physical ($p < 0.001$), bodily pain ($p = 0.039$), general health ($p = 0.01$), vitality ($p = 0.01$), social functioning ($p = 0.017$) and mental health ($p = 0.02$). A trend for differences between clinically unaffected and affected participants was observed for role–emotional ($p = 0.092$), and no statistically significant differences were found for physical functioning ($p = 0.02$). The two summary indices of the SF-36 are also reported. Before the clinic visit (baseline) affected individuals had a statistically significantly lower mean physical component score (PCS) than the clinically unaffected individuals ($p = 0.02$). This was the only time point at which there was a statistically significant difference between the mean PCS of the clinically unaffected and clinically affected groups. There were no statistically significant differences in the mean mental component scores (MCS) of the clinically unaffected and affected participants at any of the time points. Statistical analyses also confirmed that there were no statistically significant differences across the time points in the PCS for the combined group of clinically unaffected and affected participants. There was, however, a statistically significant increase in the MCS score (that is, better mental health) at the 12-month follow-up compared with baseline (no *p*-value reported). There were no statistically significant associations between baseline PCS or baseline MCS and age, sex, educational level, marital status or ferritin levels.

Power and Adams[98] report the changes in the scores of the SF-36 subscales. As the results for the two patient groups were not significantly different the groups were analysed together. Once again, the combined data are reported here, which includes data from the 25 participants identified by population screening who do not meet the inclusion criteria of this review. The vitality scale of the SF-36 significantly improved after participants were informed of their genetic test result ($p < 0.05$). The PCS also significantly improved with no significant difference in the general health score or MCS. There were no significant changes across any of the SF-36 subscales according to genetic testing result (no numerical results reported in paper and it was not possible to read values from the figure).

Study-specific outcomes used in reporting emotional reactions

Hicken and colleagues[96] report on the emotional reactions of patients after the test had been carried out. Summary scores for the outcomes of genetic testing were created by summing positive outcomes (to give a score range of 4–16) and negative outcomes (score range 8–32). Patients reported *HFE* genotyping to be as beneficial as the control subjects anticipated it would be (patient group mean 12.44 versus control group mean 13.14, $p > 0.05$), and patients found it to be less detrimental than anticipated by control subjects (patient group mean 17.56 versus control group mean 13.39, $p < 0.001$). These results are presented in a bar chart, which includes error bars to give an indication of uncertainty about the mean, and

the numerical values have been estimated from the chart. The paper does not indicate which measure of uncertainty [SD or standard error of the mean (SEM)] is indicated by the error bars. In addition to the summary measure for positive and negative outcomes the individual negative elements are also reported in a bar chart (from which the numerical values in *Table 8* and Appendix 8 have been estimated) with some *p*-values reported in the text. Control subjects expected more anxiety ($p < 0.0001$), sadness ($p < 0.0001$) and anger ($p < 0.005$) and expected to have more difficulty paying for genetic testing ($p < 0.0001$) than was reported by patients. There were no significant differences between patients and control subjects for the other negative outcomes of family conflict, job or insurance loss, discrimination and confidentiality.

TABLE 10 *Summary of outcomes of understanding of the test result*

Individual knowledge questions, Hicken et *al*. 2004[96]			
	Patients (*n* = 87) correct recall	**Control subjects (*n* = 50) correct recall**	***p*-value**
Overall recall	65%±26%	59%±30%	> 0.05
Define genetic test	48%	56%	
Interpret positive *HFE* genotype	59%	62%	
Immutability of genetic test result	65%	64%	
Phlebotomy changes iron levels	81%	86%	
Test predicts symptoms	51%	42%	
Test indicates current illness	45%	36%	
Test predicts when symptoms begin	75%	76%	
Children and siblings will have same mutation	49%	52%	
Short-answer questions, Hicken et *al*. 2004[96]			
		Correct answer	
Purpose of phlebotomy		85%	
Purpose of annual serum ferritin measurement		79%	
Definition of genetic		90%	
Difference between *HFE* genotyping and transferrin saturation test		25%	
True–false questions, Hicken et *al*. 2004[96]			
		Correct answer	
In haemochromatosis the body tends to store too much iron		98%	
There is no effective treatment for haemochromatosis		92%	
Haemochromatosis is treated by drawing blood to lower iron levels		98%	
It is not necessary to treat haemochromatosis unless the person has organ damage		96%	
Possible to have haemochromatosis and not know it		99%	
About 1 out of every 200 people has haemochromatosis		60%	
People with haemochromatosis get sick because too much iron damages organs		97%	
Untreated haemochromatosis may lead to early death		97%	
There is no cure for haemochromatosis		86%	
Haemochromatosis is less common in women		42%	

continued

TABLE 10 *Summary of outcomes of understanding of the test result (continued)*

True–false questions, Meiser *et al*. 2005[97]		
	Correct answer 2-week follow-up	**Correct answer 12-month follow-up[a]**
Regular removal of blood will avoid or reduce many of the symptoms of haemochromatosis (True)	93.2%	98.7%
A person who has two copies of the gene change for haemochromatosis is likely to develop haemochromatosis (True)	87.3%	87.2%
Hereditary haemochromatosis is uncommon (False)	85.3%[a]	75.6%
A person who has just one copy of the gene change for haemochromatosis usually will be perfectly healthy (True)	76.1%	70.5%
To be at risk of developing haemochromatosis you need to inherit one copy of the gene change from each of your parents (True)	71.2%[a]	69.9%
If a person carries two copies of the haemochromatosis gene change they have a 100% chance of passing on the two gene changes to a son or daughter (False)	54.5%[a]	67.9%
The gene change C282Y is found in most people with haemochromatosis (True)	45.2%	59.6%

Understanding of gene changes, Meiser *et al*. 2005[97]			
	Homozygous for C282Y or H63D	**Heterozygous for C282Y or H63D**	**Compound heterozygotes**
One gene change, *n* (%)	7 (16.7)	12 (63.2)	4 (23.5)
Two gene changes, *n* (%)	28 (66.7)	3 (15.8)	10 (58.8)
Unable to remember, *n* (%)	7 (16.7)	4 (21.1)	2 (17.6)

a Three values for the 2-week follow-up and all values for the 12-month follow-up were estimated from a figure in the paper.

At the 2-week post-consultation time point Meiser and colleagues[97] administered the 7-item intrusion subscale of the IES to measure the frequency and severity of intrusive thoughts about haemochromatosis. A score of 20 or higher on the intrusion subscale of the IES is considered to be strongly predictive of a significant stress response syndrome. However, only one participant scored over 20 when this instrument was administered. There was no statistically significant difference between the responses of unaffected and affected individuals.

TABLE 11 *Summary of outcomes of benefits and problems of testing*

Common perceived benefits of testing, Hicken *et al*. 2004[96]	
Improved health and prevention of future health problems	40%
Learning risk to self and family	19%
Improved understanding of health	11%
Improved psychological well-being	12%
No benefits identified	19% (*n* = 11)
Perceived detrimental effects of testing, Hicken *et al*. 2004[96]	
No problems with genetic testing identified	88% (*n* = 49)
Decreased psychological well-being	2% (*n* = 1)
Denied health insurance because of HFE genotype	2% (*n* = 1)

TABLE 12 *Summary of outcomes of compliance with treatment*

Compliance with treatment, Hicken *et al*. 2004[96]
Iron depletion was achieved in 99% of patients
Adherence to maintenance therapy in the first year was 94%
Maintenance therapy dropped by 8% each year in subsequent years
Adherence to maintenance was not associated with demographic factors, barriers to compliance or knowledge of haemochromatosis ($p > 0.05$)
The majority of patients (88%) reported few difficulties with obtaining annual serum measurements

Understanding of test result

Two studies[96,97] report outcomes related to participants' understanding of their test result (*Table 10*). This information is often embedded within, and difficult to separate from, the reporting of outcomes on participants' knowledge about haemochromatosis.

The overall recall of information by patients reported by Hicken and colleagues[96] was not significantly different from that of control subjects (patients 65%±26% versus control subjects 59%±30%, $p > 0.5$). The percentage of participants providing the correct answer to each of the individual questions that made up this outcome are also reported but if any statistical comparisons were made between patients and control subjects these are not reported. Hicken and colleagues also asked the patient cohort some short-answer and true–false questions. The short-answer questions were correctly answered by 70% of patients (range 25–90%) and the true–false questions were answered correctly by 87% (range 42–99%). Only 25% of patients could correctly answer the short-answer question about the difference between *HFE* genotyping and the TS test. Unsurprisingly the patients who could not recall undergoing an *HFE* genotyping test were less likely to understand the difference between *HFE* genotyping and the TS test ($p < 0.0001$).

In total, 101 participants in the study reported by Meiser and colleagues[97] answered seven true–false questions 2 weeks after their consultation. Two of the questions assessed their understanding of the significance of carrying one or two mutations, respectively, for haemochromatosis. Most participants responded correctly to these two questions (76.1% and 87.3%). In total, 93% of participants knew that regular removal of blood will avoid or reduce many of the symptoms of haemochromatosis. The question that fewest participants answered correctly assessed whether participants knew that the C282Y mutation is found in most people with haemochromatosis. Only 45.2% of participants knew that this was the case. Participants were asked these questions again at the 12-month follow-up. The results are presented in a figure but the study authors do not comment on whether these differed in any way to the results obtained at the 2-week follow-up. Genetic testing results were available for 95 of the 101 participants in the Meiser and colleagues study. Of the 95 participants with a genetic testing result, 80 (84.2%) had learnt of the outcome of their test before their first attendance at the clinic and entry into the study. Homozygotes and heterozygotes for C282Y and H63D, plus compound heterozygotes, were asked at the 2-week consultation whether they believed that they had one or two gene mutations, or if they could not remember. The results for 77 of these participants are reported: 69.3% were able to correctly state the number of mutations that they carried. There was no association between education level and having an accurate understanding of the number of gene changes associated with one's particular genetic testing result ($p = 0.29$), and similarly there was no association between the presence of a family history of haemochromatosis and understanding of the number of gene changes associated with the genetic testing result ($p = 0.53$).

Benefits and problems of testing perceived after test carried out

The patients in the study by Hicken[96] reported the positive benefits and negative detrimental outcomes that resulted from *HFE* genotyping on two short-answer questions (*Table 11*). The most commonly reported benefit of testing was improved health and prevention of future health problems (40% of patients). The other reported benefits were learning of the risk to self and family (19%), improved understanding of health (11%), and improved psychological well-being (12%). Eleven participants (19%) did not identify any benefit of testing. The majority of participants did not report any problems from genetic testing (88%). Decreased psychological well-being was reported

by one woman, and one man reported that he had been denied health insurance because of his *HFE* genotype.

Compliance with treatment

Hicken and colleagues[96] reported on patient compliance with treatment recommendations (*Table 12*). Compliance with therapy was defined as achieving an SF ≤20 ng/ml after undergoing serial phlebotomy for iron overload. Iron depletion was achieved in 99% of patients. However, after achieving iron depletion, adherence to maintenance therapy in the following years dropped. In the first year after achieving iron depletion 94% adhered to maintenance therapy but this dropped by 8% each year in subsequent years. Adherence to maintenance was not associated with demographic factors, barriers to compliance or knowledge of haemochromatosis ($p > 0.05$). The majority of patients (88%) reported few difficulties with obtaining annual serum measurements.

Meiser and colleagues[97] reported that, at the 12-month follow-up, all participants for whom iron studies are recommended (homozygotes and compound heterozygotes) reported having ever had iron studies, and 96% reported having had iron studies in the past year. At the 12-month follow-up 62% of those participants who had increased SF at baseline reported ever having had a venesection, and 57% reported having undergone a venesection in the past year, which included any that may have been carried out at the actual clinic visit. However, it is important to note that 39 participants (38.6%) had been lost to follow-up by the 12-month time point.

Summary of psychosocial aspects of DNA testing

- Evidence on the psychosocial aspects of DNA testing is limited in quality and quantity. Only three cohort studies met the inclusion criteria for the review and each study assessed and reported on the psychosocial outcomes of genetic testing for *HFE* in a different way.
- All of the studies had methodological limitations. Sampling and blind assessment were not discussed or reported in any of the studies. Only one study clearly reported objective eligibility criteria and sample attrition; in the other two studies eligibility criteria were unclear and reporting of sample attrition was incomplete, therefore the studies may have sampling and measurement bias. The studies were small and the generalisability of these studies to the UK population is difficult to determine.
- Generally the results suggest that genetic testing in the case of haemochromatosis is viewed positively and is well accepted. Genetic testing is accompanied by few negative psychosocial outcomes and may lead to reduced anxiety.
- One cohort study[96] with a control group sought opinions from people who had been *HFE* genotyped on average 3 years before the study took place. Control subjects expected to experience statistically significantly more anxiety, depression and anger related to a positive genetic test than was reported by patients.
- One study[97] assessed psychological distress levels in participants before and after attendance at a haemochromatosis clinic and compared patients clinically affected by haemochromatosis with those clinically unaffected. No statistically significant differences were seen between clinically affected and clinically unaffected participants at any time point for generalised anxiety scores (STAI) or intrusive thoughts. Clinically affected participants had significantly lower scores on the SF-36 PCS at baseline than unaffected participants but scores were no longer significantly different at 12 months post consultation. STAI-State and PCS did not change across time points for both clinically affected and clinically unaffected participants combined, although a statistically significant increase in the SF-36 MCS (i.e. better mental health) was observed at the 12-month follow-up. The mean IES scores suggest only moderately high levels of intrusive thoughts after genetic testing.
- One study[98] assessed psychological effects before and after genetic testing using the STAI and SF-36. There were significant improvements in the vitality subscale of the SF-36 and the PCS after participants were informed of their genetic test result. There were no significant differences in the general health score or the MCS before and after participants had received their genetic test result. No significant deleterious psychological effects were found on anxiety; anxiety significantly decreased in homozygotes and heterozygotes after genetic testing and remained constant in C282Y mutation-negative cases (possibly because no explanation had been found for their presenting symptoms).

Chapter 7
Economic evaluation

Introduction

The aim of this chapter is to evaluate adding DNA testing to existing diagnostic strategies for detecting HHC in groups of patients suspected of having the disorder and family members of patients with haemochromatosis. A systematic review of the literature was conducted to identify economic evaluations on the use of genotypic tests for the detection of HHC. An economic model was developed to compare diagnostic algorithms and family testing strategies with and without DNA testing. Sections in this chapter will report the results of the systematic review and outline the components of the economic evaluations, including the structure of the economic model, the sources of information for costs and benefits and the results of the analysis.

Systematic review of the literature

A systematic review of the literature was undertaken to identify economic evaluations on the use of genotypic tests for the detection of HHC. The methods for the systematic review are described in Chapter 3. The details of the inclusion and exclusion criteria are shown in Appendix 1 and the search strategies are shown in Appendix 2.

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by two reviewers. The full text of relevant papers was obtained and inclusion criteria were applied by a health economist and a reviewer. Differences in opinion were resolved through discussion or by arbitration by a third reviewer if necessary.

Economic evaluations were eligible for inclusion if they reported on the cost or cost-effectiveness of comparing DNA tests with other diagnostic strategies including quantitative phlebotomy or other iron studies and liver biopsy for Caucasians with clinical suspicion of iron overload or relatives of suspected cases (Appendix 1). Specialist clinic-based patient groups (e.g. diabetic clinics) and population screening studies were excluded.

Quantity and quality of research

The literature search identified two published economic evaluations that met the inclusion criteria.[99,100] Studies that were assessed and excluded are shown in Appendix 3 with their reasons for exclusion. El-Serag and colleagues[99] estimated the cost-effectiveness of screening for HHC in family members using genotypic tests compared with phenotypic tests and no screening in the USA. Adams[100] investigated the likely cost of genotyping spouses and whether this would reduce the number of investigations of children in Canada. The quality of these economic evaluations has been assessed using a standard checklist adapted from Drummond and Jefferson[82] (*Table 13*) and the two studies are discussed in more detail below.

Both studies clearly defined the study question and explained the competing alternatives. They each used the correct comparator and the patient group of interest was clearly stated and appropriate. Furthermore the study type appeared reasonable: Adams[100] used a cost-minimisation model and El-Serag and colleagues[99] used a cost–utility model. Both studies were conducted in North America and so it is unclear how these studies relate to the UK NHS.

Adams[100] did not consider long-term costs and consequences. El-Serag and colleagues[100] used a lifetime horizon and estimated incremental cost-effectiveness with appropriate discounting rates. They also presented sensitivity analyses of the key parameters. It is unclear whether the studies valued the costs and consequences appropriately. Adams[100] does not report the source of costs used in the study or how these costs were derived. El-Serag and colleagues[100] seem to have included all of the costs relevant to HHC and screening; however, these have been taken from earlier studies and have not been adjusted for time. The data used in the model have not been discussed and in many cases the sources of the data have not been given. The

TABLE 13 *Methodological quality of reporting of the cost-effectiveness studies*

Quality criteria	El-Serag et *al.* 2000[99]	Adams 1998[100]
Is there a well-defined question?	Y	Y
Is there a clear description of alternatives (i.e. who did what to whom, where and how often)?	Y	Y
Has the correct patient group/population of interest been clearly stated?	Y	Y
Is the correct comparator used?	Y	Y
Is the study type reasonable?	Y	Y
Is the perspective of the analysis clearly stated?	Y	U
Is the perspective employed appropriate?	U	U
Is the effectiveness of the intervention established?	Y	Y
Has a lifetime horizon been used for analysis and if not has a shorter time horizon been justified?	Y	n/a
Are the costs and consequences valued credibly?	U	U
Is differential timing considered?	Y	N
Is incremental analysis performed?	Y	N
Is sensitivity analysis undertaken and presented clearly?	Y	N
Were credible conclusions drawn from the results	Y	Y

Y, yes; N, no; U, unclear; n/a, not applicable.

conclusions in both of the studies appear credible from the results presented.

Results of the published economic evaluations

A summary of the results of the published economic evaluations is shown in *Table 14*.

Adams[100] estimated the costs of genotyping spouses of homozygotes to reduce the number of investigations of children. Costs were estimated for genotyping all children of homozygotes compared with genotyping spouses and then genotyping children if the spouse was a heterozygote or homozygote. If the spouse was not a homozygote or heterozygote, investigations in the children would be unnecessary.

A total of 291 children of homozygotes were investigated using TS, SF and genetic tests. Costs incurred in the phenotypic strategy were CDN$58,200. In total, 13 of these children were found to be homozygotes in 116 families with the C282Y mutation. In the spousal strategy 116 spouses were genotyped with subsequent investigation of 22 children at a total cost of CDN$35,600. Therefore the genotyping of the spouses reduced the number of investigations in children from 291 to 22 with a cost saving of 39%.

El-Serag and colleagues[99] developed a decision tree model to evaluate screening strategies for HHC in siblings and children of affected patients. They assumed that a proband had been confirmed to have HHC on the basis of standard phenotypic criteria. It was estimated that 5% of the children would be homozygous, assuming that the proband was homozygous and 25% of siblings were homozygous. The model estimated the life expectancy, qualify of life and costs for various screening strategies, and incremental cost-effectiveness ratios were calculated compared with no screening. For the no screening strategy, life expectancy was estimated based on previous studies, including that of Adams and colleagues.[11] The serum iron studies strategy entailed measuring TS and SF levels in relatives of the proband. Screening of children was assumed to start at 10 years of age and continue until 40 years of age or until an abnormal test result was found. Siblings were screened once with repeated testing in people with elevated values.

There were three strategies for genetic testing. In the first genetic testing strategy, the proband was tested first and, if found to be homozygous, the spouse was tested. Children were gene tested if the spouse was heterozygous. Children homozygous for C282Y underwent iron studies. If a child was found not to be homozygous no further screening was

TABLE 14 *Summary of cost-effectiveness studies*

	Adams 1998[100]	**El-Serag *et al.* 2000[99]**
Location	Canada	USA
Strategy	Genotyping spouse of proband homozygote with HHC and if homozygous or heterozygous gene testing children compared with genotyping all children of homozygous proband (phenotypic strategy)	No screening among siblings and children Screening using serum iron studies Gene testing proband followed by gene testing spouse Gene testing proband followed by gene testing siblings and children Gene testing siblings and children before the proband
Study type	Cost-minimisation model	Cost-effectiveness decision tree model
Study group	Children and spouses of an affected proband with HHC; 291 children of 121 homozygotes	Hypothetical cohort of siblings and children of an affected proband with HHC
Results	Phenotypic strategy: 291 children investigated; costs incurred CDN$58,200 Genotyping spouse strategy: 116 spouses and 22 children genotyped; costs incurred CDN$35,600 Cost saving 39% by genotyping spouse	Screening children: screening using iron studies ICER US$7934/LYS; gene testing proband followed by spouse (for two or more children) ICER US$3665/LYS; gene testing proband followed by one child ICER US$508/LYS; gene testing children before proband ICER US$12,277/LYS Screening siblings: all screening strategies were dominant compared with no screening; screening with iron studies was the most expensive; gene testing of siblings first had lower costs when only one sibling was tested; for two or more siblings, gene testing proband first was less costly
Conclusion	Genotyping the spouse of a homozygote is the most cost-efficient strategy in pedigree studies because it leads to more selective investigation of children for the HHC gene	Gene testing is a cost-effective method of screening relatives of patients with HHC

CDN$, Canadian dollars; ICER, incremental cost-effectiveness ratio; LYS, life-years saved

performed. If the proband was not homozygous the child would undergo iron studies.

The next strategy was similar to the first one except that the spouse was not gene tested. The proband was gene tested followed by gene testing of the children or siblings if the proband was homozygous. Relatives who were homozygous then underwent iron studies. As before, if the proband was not homozygous the relative would undergo iron studies.

In the final genetic testing strategy the relatives were gene tested before the proband. Those relatives who were homozygous underwent iron testing. If the relative was not homozygous, then the proband was gene tested and the relative underwent iron studies if the proband was homozygous.

Strategies using gene testing were less costly than serum iron studies. Compared with no screening, gene testing the proband followed by testing of a child was the least expensive and most cost-effective strategy for one child (incremental cost-effectiveness ratio US$508 per life-year saved). For screening two or more children, gene testing the spouse if the proband was homozygous was the most cost-effective strategy. Compared with the no screening strategies for siblings, all strategies cost less and yielded greater benefits.

El-Serag and colleagues[99] performed sensitivity analyses for the costs of the tests, screening frequency and proportions of probands with *HFE* gene mutations. For all sensitivity analyses, *HFE* gene testing remained cost-effective.

SHTAC economic model

The economic evaluations identified in the systematic review were of reasonable quality but, as discussed above, were not able to answer the current research question. In particular there were concerns about the generalisability of the

evaluations to the UK and incomplete description of data sources. The strategy of testing the spouse of the proband as outlined in one of the studies has the consequence of identifying carriers from the general population and therefore merges into population screening. In addition, this strategy was most efficient when there were more than two offspring but the UK current birth rate is less than two (see Chapter 8, Other relevant factors). As a consequence it was decided to develop a de novo economic model to evaluate diagnostic testing strategies for HHC in the UK. The models identified in the systematic review provided a useful background and basis for developing this model, although other sources of data/information were required.

A comparison of the costs and consequences of testing strategies for the diagnosis of haemochromatosis was made using decision-analytic models. Models were constructed in Microsoft EXCEL for diagnosing HHC in people suspected of having haemochromatosis and in family members of patients diagnosed with haemochromatosis. The models were constructed according to standard modelling methods.[101]

Costs were derived from primary data from previous studies and from national and local NHS unit costs. Only direct NHS costs were included and hence the model was from the perspective of the NHS. The time horizon chosen for the model was for the testing and treatment period only. It was decided not to model lifelong costs and consequences of the diagnostic decision because (1) long-term data on the natural history, prognosis and quality of life of patients with haemochromatosis is poor and (2) the strategies chosen detect the same numbers of patients with haemochromatosis and so a cost-minimisation model is appropriate.

The economic evaluation focused on estimating the number of cases detected by the diagnostic strategy, the number of cases treated and the resources used. The outcome is reported as cost per case detected as this outcome is of most interest to the NHS. Differences in costs between the strategies are also reported.

The structure and data inputs of all of the decision trees were informed by systematic literature reviews (Chapter 4), clinical guidelines and the results of systematic searches (Appendices 1 and 10) and discussion with clinical experts.

Economic model structure

The addition of DNA testing to diagnostic algorithms in people suspected of having haemochromatosis

Before the discovery of the common gene mutations, diagnosis of HHC was based on clinical suspicion, including persistently raised TS and SF with no other diagnosis followed by liver biopsy. Since the identification of the gene it has been possible to use DNA testing to confirm the diagnosis in those in whom it is suspected. Liver biopsy then becomes a prognostic test in those suspected of having liver damage and can be avoided in those with raised iron levels and no biochemical evidence of liver damage.

Decision models were constructed to compare the costs and consequences of two diagnostic algorithms in people suspected of having HHC on the basis of persistently raised TS > 45% and SF > 300 µg/l.[72] The algorithms for people with suspected HHC are liver biopsy for all people and genetic testing for all people. The end point of both algorithms is detection of a case requiring treatment according to current clinical guidelines and the reported outcome will be cost per case detected. The goal of a diagnostic strategy is to improve patient management and ultimately patient outcomes. The advantage of the genetic testing strategy is that it avoids the use of liver biopsy.

The decision tree is shown in *Figure 2*. For the liver biopsy strategy all patients have liver biopsy and are either confirmed positive or negative phenotypic haemochromatosis. Those who are positive will be treated for haemochromatosis and those who are negative will not.

For the DNA testing strategy all people receive a DNA test, which will be either positive (YY, C282Y homozygous) or negative. Those who are YD compound heterozygous (C282Y/H63D) will be treated in the same way as those who have a negative DNA test. This assumption was made based on clinical guidelines and expert clinical opinion and was a pragmatic approach in view of the limited data on the long-term prognosis and treatment of YD compound heterozygous patients. All patients with raised SF (> 1000 µg/l) receive a liver biopsy to check for liver cirrhosis. All patients with a positive DNA test will be treated as they are assumed to have HHC. Patients with a negative DNA test and SF < 1000 µg/l are monitored and receive a repeat SF test. If their SF is stable or

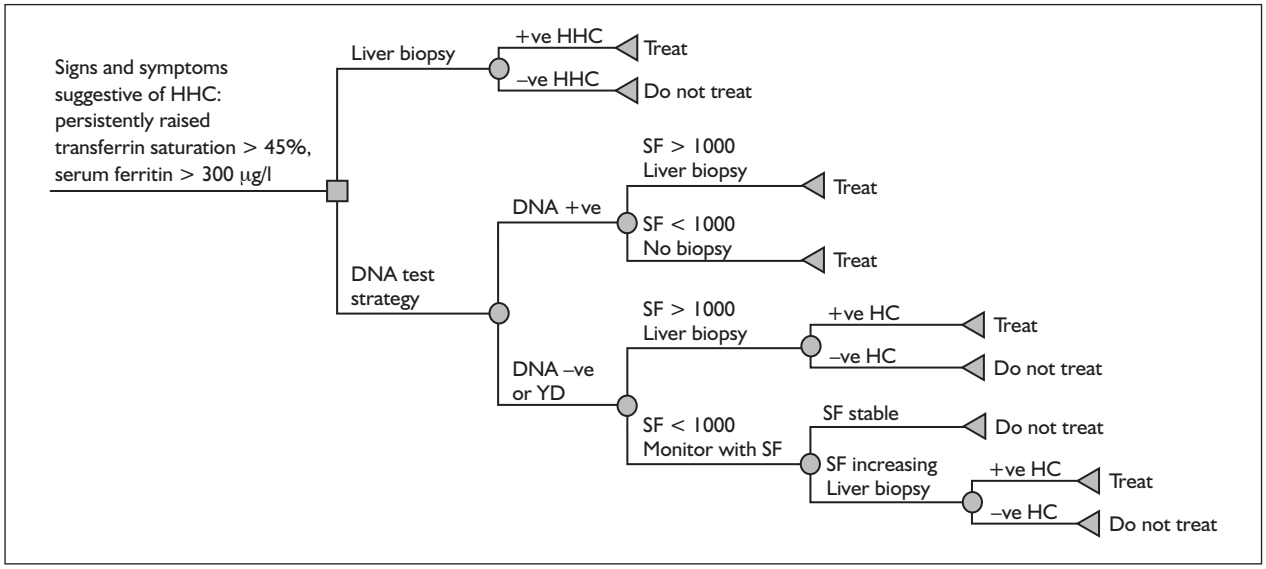

FIGURE 2 *Decision tree for DNA testing in people suspected of having haemochromatosis. HC, haemochromatosis; LB, liver biopsy; SF, serum ferritin; YD, compound heterozygous C282Y/H63D.*

decreasing then they are not treated, whereas those with increasing SF have a liver biopsy to confirm haemochromatosis. Those with confirmed haemochromatosis will be treated.

The model can be run for different strategies for different TS and SF levels. For the purpose of the model a 'typical' patient is defined who is representative of all patients. For the baseline run it is assumed that a typical patient is a 45-year-old man because clinical HHC is more common in men and raised iron levels will typically appear during the middle of the fourth decade of life. The effect of patient age or gender is investigated in the model through the use of sensitivity analyses.

DNA testing for family members of people diagnosed with haemochromatosis

Separate decision models were constructed to compare the costs and consequences of two testing algorithms in family members of people diagnosed with HHC. The algorithms for testing family members are biochemical testing for all versus genetic testing for all. The end points of the algorithms are detection of a case requiring treatment according to current clinical guidelines, identification of family members at risk for HHC who need to be monitored and identification of family members who are not at risk for HHC. These outcomes will be incorporated into the model by considering unnecessary investigation of those with false-positive diagnoses and missed diagnoses.

The decision tree is shown in *Figure 3*. For the biochemical test strategy relatives have SF and TS tests. If they have raised iron levels (positive biochemical tests results, i.e. TS > 45% and SF > 300 μg/l) according to clinical guidelines,[72] they are treated; if not they will be monitored to see if their iron levels increase. If the iron levels increase, they will be treated for HHC.

For the DNA test strategy relatives have a DNA test. Those with a positive result (YY, homozygous C282Y) have biochemical tests and those with raised iron levels (positive biochemical tests results, i.e. TS > 45% and SF > 300 μg/l) are treated.[72] Those who do not have raised iron levels (negative TS and SF results) are monitored to see if their iron levels increase; if they do increase they will be treated for HHC, and if they do not they will not be treated. Those without a positive DNA test for C282Y will not need treatment or any further medical investigation for HHC.

For the purpose of the model a typical patient is defined who is representative of all patients. Siblings will be assumed to be over 45 years of age because most new probands will be over 45 years of age at diagnosis. Those who are monitored will be retested once according to clinical advice. Similarly, a typical child will be aged 25 years as there is a presumption against testing children for conditions that do not directly affect them during childhood.[102] At this age most will not have manifestations of iron overload but we assume that

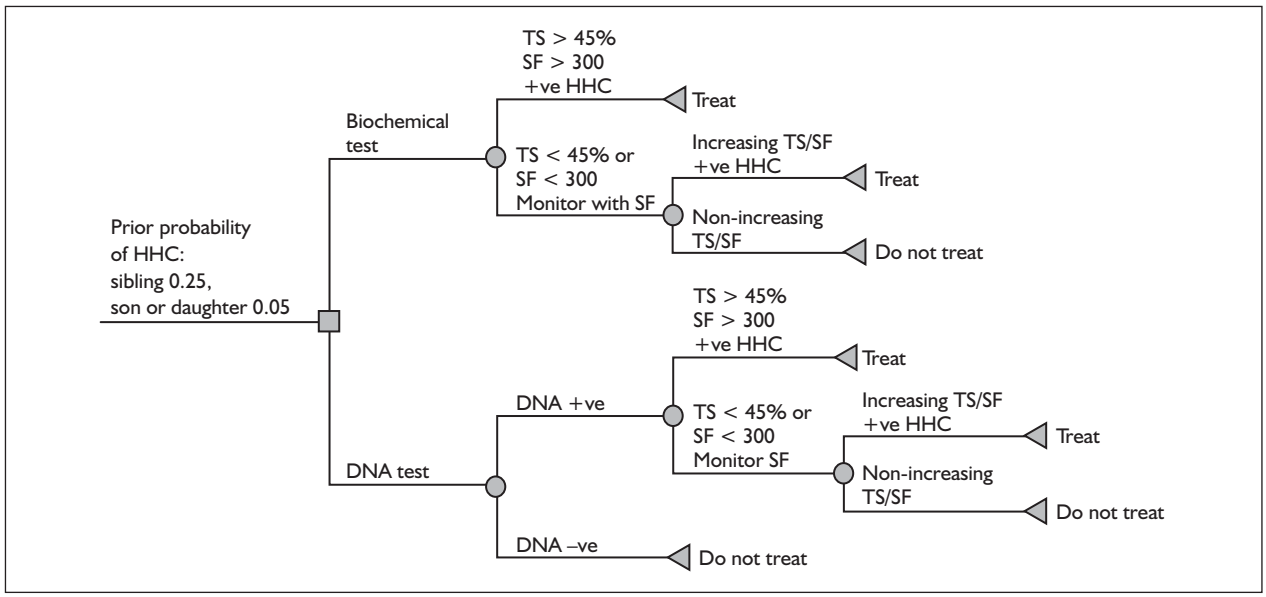

FIGURE 3 *Decision tree for the use of DNA testing in family members. SF, serum ferritin; TS, transferrin saturation.*

those who develop symptoms of iron overload will do so within 20 years and that the proportion of children with increased iron levels will rise linearly over this time period. The children will be tested every 5 years until iron overload is detected, i.e. a maximum of five times.

Data sources used in the models

This section describes the inputs to the models, provides justification for their use, details their respective sources and explains their role in the models. The data used in the models have been collected from systematic reviews and systematic searches discussed in more detail in Chapter 4 and Appendix 1. Data sources were chosen for the models on the basis of appropriateness to the UK and the quality of the data as assessed by the reviewers and in consultation with clinical experts.

The literature shows that a range of thresholds is used for the diagnostic tests, and there is a wide range of results in the accuracy of these tests. *Table 15* shows the data used in the models and also the ranges of other data found in the systematic searches (Appendix 10). These ranges were used to inform appropriate sensitivity analysis ranges. The thresholds used here for modelling are TS > 45% and SF > 300 µg/l, as used in clinical guidelines.[72] The effect of using different thresholds has been shown as a sensitivity analysis below (see *Table 22*). The sensitivity and specificity for TS was also taken from the clinical guidelines.[72] The sensitivity and specificity of SF was taken from Moodie and colleagues[61] as this UK study reported values for different thresholds of SF separately for men and women. Liver biopsy is used as the gold standard for confirming diagnosis from SF and TS tests and so the model assumed that liver biopsy was 100% accurate in diagnosing HHC.

Table 16 shows the key inputs to the SHTAC decision tree models and the ranges of these parameter values found in the data searches. The decision tree for people suspected of having haemochromatosis required an estimate of the prevalence of HHC in those who are referred with symptoms of HHC. The data for prevalence for this population was scarce with only one relevant study found.[61] The prevalence of HHC in a population with suspected iron overload was estimated from this study of 427 patients referred for investigation of liver disease from an ethnically mixed population in south London.[61] The prevalence was estimated by excluding those of Afro-Caribbean, African, Asian or Mediterranean origin, including only those with northern European or Celtic origins. The prevalence of HHC in relatives is estimated using simple genetic theory.

Although liver biopsy was associated with a small risk of death and other complications, for the base case we assumed that there were no deaths or major events from liver biopsy as in other modelling studies.[104]

Vantyghem and colleagues[94] described the makeup of 156 subjects recruited in the Endocrinology and

TABLE 15 *Sensitivity and specificity of diagnostic tests for haemochromatosis*

	Sensitivity (range)	Specificity (range)	Source
TS > 45%[a]	94% (64–100%)	94% (73–100%)	Olynyk *et al*. 1999[103]
SF > 300 μg/l[a]	73% (50–96%)	85% (85–87%)	Moodie *et al*. 2002[61]
SF > 200 μg/l[a]	73% (70–97%)	70% (70–94%)	Moodie *et al*. 2002[61]
Liver biopsy[b]	100%	100%	Assumption

a Accuracy of biochemical tests for detecting haemochromatosis.
b Accuracy of liver biopsy for detecting haemochromatosis.

TABLE 16 *Key inputs to SHTAC economic model*

	Input value[a]	Reference/comment
Prevalence of HHC		
Population with suspected iron overload	0.038	Moodie *et al*. 2002[61] from liver clinic
Siblings	0.25	Mendelian
Children	0.05	0.5 × 1 in 10
Among patients with HHC	91.3% (range 90–100%)	UK HHC Consortium 1997[38]
Among the general population	0.99% (range 0–1.24%)	UK HHC Consortium 1997[38]
Liver biopsy		
Death	0	Assumption
Bleeding requiring transfusion	0	Assumption
For diagnostic pathways tree		
Proportion with raised SF > 1000 μg/l (DNA positive)	39% (range 48%)	Vantyghem *et al*. 2006[94]
Proportion with raised SF > 300 μg/l and < 1000 μg/l (DNA positive)	61% (range 48%)	Vantyghem *et al*. 2006[94]
Proportion with raised SF > 1000 μg/l (DNA negative)	24%	Vantyghem *et al*. 2006[94]
Proportion with raised SF > 300 μg/l and < 1000 μg/l (DNA negative)	76%	Vantyghem *et al*. 2006[94]
For family testing tree		
Penetrance of HHC men	76%	McCune *et al*. 2006[60]
Penetrance of HHC women	32%	McCune *et al*. 2006[60]
Proportion of offspring with HHC who initially have iron overload	20%	Assumption

SF, serum ferritin.
a Range shows the range of alternative data sources found for the parameter.

Metabolism Department of Lille University who were referred because of general symptoms of iron overload and abnormal iron levels (SF > 300 μg/l or TS > 45%). Amongst other data they reported the numbers who were homozygous for the C282Y mutation with high SF (> 1000 μg/l).

Penetrance is the proportion of people homozygous for C282Y who go on to develop manifestations of the disease. The penetrance depends on the definition of disease (biochemical variables or fibrosis, etc.) and hence the value for the penetrance varies widely.

Costs

As the analysis reflects an NHS perspective, UK-specific resource use and costing data have been used when available. Cost data were obtained from a number of primary and secondary sources (*Table 17*).

The UK Genetic Testing Network (UKGTN; www.ukgtn.org) provides information on genetic testing in the UK, including information on costing for DNA tests from different UK laboratories for different diseases and genes. Seven laboratories on the GTN website provide information on the cost of the genetic test for HHC, with the average cost approximately £100 (range £23.60–£140). Based on advice from clinicians we assumed that patients' consultations with a nurse or consultant would last 15 and 30 minutes respectively, and that patients would have one consultation with the nurse and consultant for the DNA test, liver biopsy or iron test. Furthermore we assumed that patients with clinical manifestations of disease would require approximately 20 venesections to remove iron from the blood and then maintain iron levels and that they would be seen about seven times by a consultant over a 5-year period.[105,106] The time taken to correct a false diagnosis will vary and such patients often receive a liver biopsy to confirm diagnosis. For this reason we assumed that people incorrectly diagnosed with HHC will have similar treatment costs to those correctly diagnosed. We further assumed that adults who are monitored will receive further iron tests and appointments with the nurse and consultant. The day-case cost for liver biopsy was derived from the Southampton General Hospital Trust and included costs for the procedure and accompanying blood tests.[107]

Results

Each of the decision tree models shown in Figures 2 and 3 were run with the parameters discussed in the sections above. The models estimated the number of patients detected with HHC and the numbers treated and monitored as appropriate. Cost data were used to estimate the total resource costs for each strategy and the strategies were compared according to cost per case of HHC detected.

Diagnostic tests in people suspected of having haemochromatosis

The results for the diagnostic test decision tree are for an average man of 45 years of age (as it is assumed that HHC will have become manifest by this age). The flow diagram (*Figure 4*) illustrates the diagnostic process and shows the numbers of people that are treated. The results in this section are presented per 100 people who have a positive TS and SF result (shown in dotted lines in the flow diagram). Based on the chosen accuracy of the diagnostic tests, there will be 100 positive test results for TS and SF for every 2880 people tested for suspected iron overload. Out of these 2880 people, 109 actually have HHC. Of those 100 people with positive test results, 75.1 are true positives (i.e. the PPV of the combined test is 75.1%). A total of 2780 people have a negative test result. Of these, 34.3 actually have the disease and are missed by the biochemical tests.

Table 18 shows the results for the diagnostic tests decision tree, comparing liver biopsy with DNA testing for 100 people with signs and symptoms of iron overload and a positive test result for TS and SF. Each strategy detects a similar number of cases (75.1) and misses 1.2 per 100 tested with the initial

TABLE 17 *Cost data used in the haemochromatosis decision tree models (price year 2006)*

Description	Cost	Source
DNA test laboratory[a]	£100	UKGTN[108]
Iron test laboratory[a]	£11.70[b]	Shepherd *et al*. 2006[107]
Venesection treatment (15 minutes)[a]	£8.75	Curtis and Netten 2006[109] (Band 5)
Liver biopsy day case[a]	£388.05	Shepherd *et al*. 2006[107]
Nurse appointment (15 minutes)	£8.75	Curtis and Netten 2006[109] (Band 5)
Surgical consultant appointment (30 minutes)	£39.00	Curtis and Netten 2006[109]
Number of treatments	20	Assumption – clinical opinion
Number of monitoring, children	5	Assumption – clinical opinion
Number of monitoring, sibling	1	Assumption – clinical opinion

a Cost does not include consultant and nurse appointment costs.
b Cost for serum ferritin or transferrin saturation test.

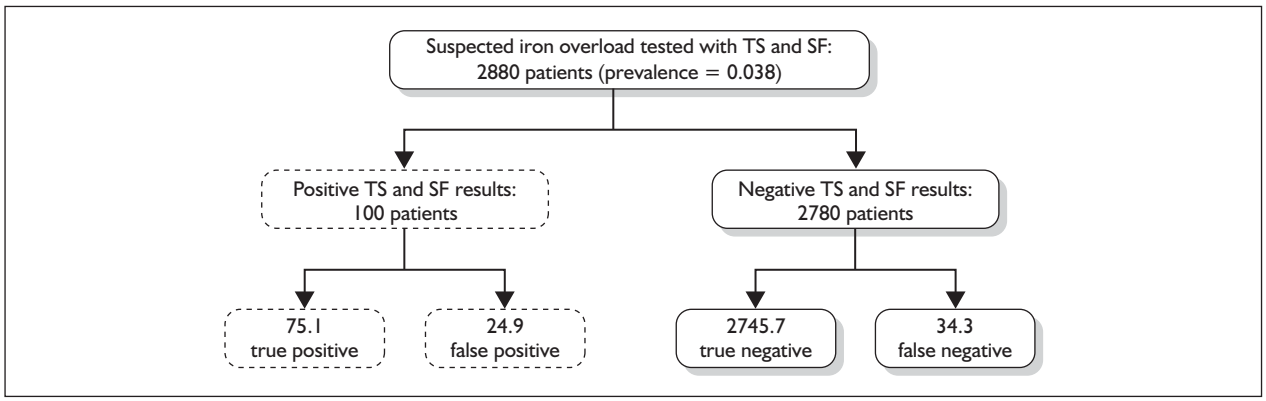

FIGURE 4 *Flow diagram of diagnostic tests (based on TS sensitivity = 94%, TS specificity = 94%, SF sensitivity = 73%, SF specificity = 85%, prevalence = 0.038, see* Tables 15 *and* 16*). SF, serum ferritin; TS, transferrin saturation.*

TABLE 18 *Base-case results for the diagnostic pathways decision tree, per 100 people with a positive test*

	Liver biopsy, *n*	Cases detected, *n*	Monitor, *n*	Total cost, £	Cost saving/ person tested, £	Cost saved/case detected, £
Liver biopsy	100.0	75.1	0	83,068		
DNA strategy	41.1	75.1	22.9	73,823	92.45	123

TS and SF test as shown in *Figure 4*. Of those with a positive test result for TS and SF, 75.1% actually have HHC. In the liver biopsy strategy everyone receives a liver biopsy, whereas in the DNA strategy only those with a negative DNA test for HHC or high SF receive a liver biopsy. Some of those with a negative DNA test are monitored to see if their SF increases. Thus, the DNA strategy has fewer liver biopsies performed but more patients will be monitored than in the liver biopsy strategy. The extra costs for liver biopsy are more than the extra costs of monitoring patients and DNA tests and so the DNA strategy will be cost saving.

The results vary according to the prevalence of the disease and the accuracy of the biochemical tests. This is illustrated by varying the PPV of the tests. PPV is the proportion of those with a positive biochemical test who have the disease, and it is dependent upon the prevalence of disease and the sensitivity and specificity of the tests:[110]

$$\text{PPV} = (\text{sensitivity})(\text{prevalence})/[(\text{sensitivity})(\text{prevalence}) + (1-\text{specificity})(1-\text{prevalence})]$$

If the PPV increases, the number of cases detected increases and the number of cases monitored in the DNA strategy decreases, because there are fewer people with a negative DNA test. If the PPV decreases, the converse happens. The number of liver biopsies performed in the DNA strategy stays fairly constant irrespective of the PPV even though they may be in different arms of the decision tree shown in *Figure 2*. The total cost saving for both scenarios is similar at around £90 per person referred. Thus, the cost saving per case detected is higher when fewer cases are detected.

This is illustrated in *Table 19* with a hypothetical PPV of 80%, for example through an increased prevalence of 0.05, in which case the cost saved per case detected is £115. With a hypothetical PPV of 44%, for example through a prevalence of 0.01, the cost saved per case detected is £216 (*Table 20*). The results are not greatly influenced by changes in costs related to the other parameters.

Sensitivity analyses

The parameters in the diagnostic pathways decision tree were varied in a series of sensitivity analyses and the results are shown in *Table 21* and *Figure 5*. When possible the parameters were varied according to the ranges from the confidence intervals of these parameters, otherwise a suitable range was chosen after discussion with experts. The sensitivity analyses show that the conclusions from the decision tree are robust across all reasonable parameter ranges, that is, the DNA strategy is cost saving compared with the baseline strategy using liver biopsy. The results were most sensitive to the

TABLE 19 *Base-case results for the diagnostic pathways decision tree with a positive predictive value of 0.8*

	Liver biopsy, *n*	Cases detected, *n*	Monitor, *n*	Total cost, £	Cost saving/ person tested, £	Cost saved/case detected, £
Liver biopsy	100.0	80.1	0	85,687		
DNA test	41.8	80.1	19.4	76,467	92.20	115

TABLE 20 *Base-case results for the diagnostic pathways decision tree with a positive predictive value of 0.44*

	Liver biopsy, *n*	Cases detected, *n*	Monitor, *n*	Total cost, £	Cost saving/ person tested, £	Cost saved/case detected, £
Liver biopsy	100.0	43.5	0	66,465		
DNA test	37.1	43.5	45.2	57,060	94.05	216

TABLE 21 *Sensitivity analyses for the diagnostic pathways decision tree*

	Inputs			Cost saved/case detected, £		
Variable	Base case	Low[a]	High[a]	Low[a]	High[a]	Range
Proportion raised SF > 1000 µg/l, DNA +ve	0.39	0.22	0.56	190	57	133
TS specificity, %	94	75	99	224	97	127
Costs liver biopsy test, £	388.05	310.44	465.66	62	184	122
Prevalence in suspected iron overload	0.038	0.016	0.06	169	111	58
Costs DNA test, £	100	80	120	150	97	53
SF specificity, %	85	75	99	144	93	51
Prevalence of genetic mutation	91.3	90	100	119	150	31
SF sensitivity, %	73	50	99	151	122	29
Proportion raised SF > 1000 µg/l, DNA –ve	0.24	0.16	0.32	132	115	17
TS sensitivity, %	94	75	99	131	122	9

SF, serum ferritin; TS, transferrin saturation.
a Results in the 'low' and 'high' columns use inputs from corresponding columns to give the range; the base-case results are shown in *Table 18*.

specificity of the TS test, the cost of the liver biopsy test and the proportion of people with a positive DNA test for the C282Y mutation and raised SF. Results were also estimated for cost per person tested. The cost saved per person tested varied between £47 and £138 for changes in the cost of the liver biopsy but it changed little for changes in TS specificity.

Changing the threshold for the biochemical tests

The threshold values for positive TS and SF tests in the decision tree were based upon those suggested in guidelines. However, other thresholds have been suggested in the literature. Therefore a sensitivity analysis was performed to investigate the effect of changing the threshold values for the biochemical tests. Adams and Chakrabarti[111] reported the accuracy of the TS test for different thresholds of 40%, 46% and 55%. *Table 22* shows the effect of using these different thresholds for TS. With a higher threshold there are fewer positive test results for TS, fewer people have SF tests and thus more people with the disease are missed. In fact, more of those with positive test results have the condition (PPV). For example, with a TS threshold of 55%, the PPV is 100% and the cost saved per case detected is £91. On the other hand, with a threshold of 40%, the PPV is 70% and the cost saved per case detected is £135.

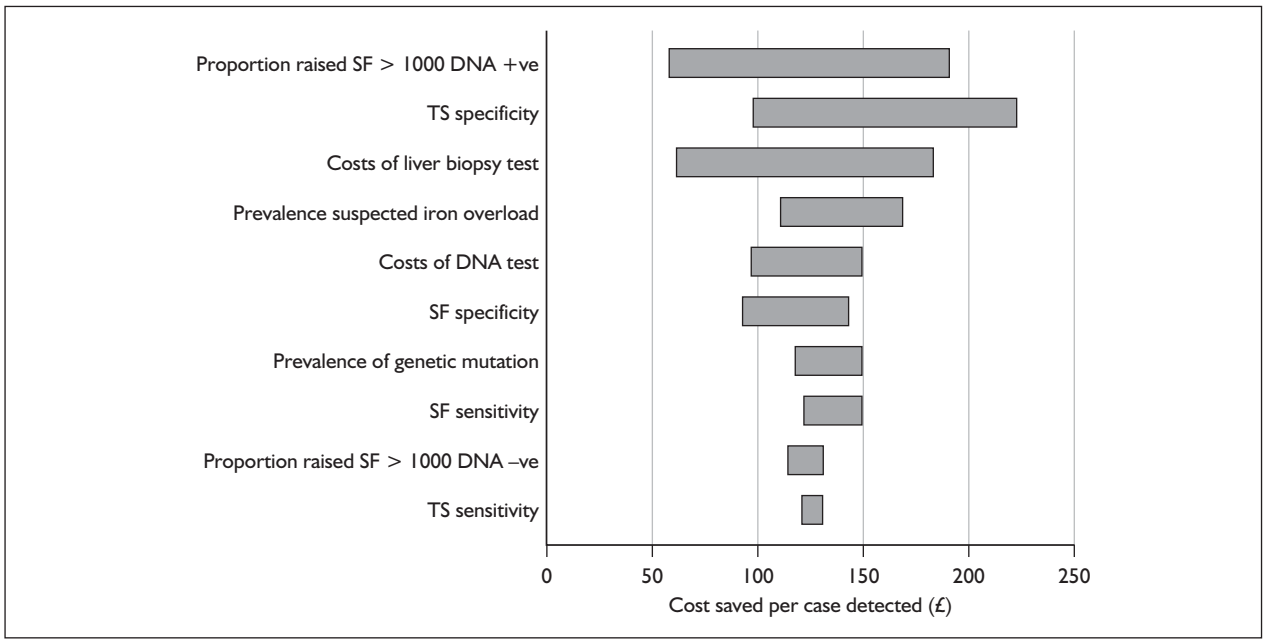

FIGURE 5 *Tornado plot for sensitivity analyses for the diagnostic pathways decision tree. SF, serum ferritin; TS, transferrin sensitivity.*

TABLE 22 *Model results using different thresholds for transferrin saturation*[a]

Threshold	Sensitivity of TS, %	Specificity of TS, %	Positive TS and SF, *n*	Negative TS and SF, *n*	True positive, *n* (PPV)	False negative	Cost saved/case detected, £
40%	92	92	37	963	26 (70%)	12	135
46%	89	95	32	968	25 (78%)	13	119
55%	77	100	21	979	21 (100%)	17	91

PPV, positive predictive value; SF, serum ferritin; TS, transferrin saturation.
a For 1000 patients tested with TS and SF.

The decision tree model was run for 45-year-old women. In this group a threshold for SF of 200 µg/l has been suggested in the literature.[72] Using this threshold with other parameters unchanged there were 60.1 cases detected and there was a cost saving per case detected for the DNA strategy of £155.

Family testing

Siblings

Table 23 shows the results from the family testing decision tree model (*Figure 3*) for male siblings of 45 years of age. The biochemical strategy tests all siblings with biochemical tests whereas the alternative strategy uses DNA tests. Each strategy detects 19% and misses 6% of cases of HHC. More people without HHC are treated and monitored in the biochemical testing strategy than with the DNA test strategy because those with negative biochemical tests are monitored. In the DNA strategy, although fewer people are monitored, the cost is higher than the cost of the biochemical strategy because the cost of monitoring is much cheaper than the cost of the DNA test. If the cost of the DNA test were to fall from £100 to £60, the DNA strategy would be the cheaper one. If those who were monitored were tested twice (instead of only once), the DNA strategy becomes cost saving (£79 per case detected).

An alternative strategy was run for the biochemical tests. In this case, if relatives have raised iron levels, i.e. TS > 45% and SF > 300 µg/l, they will be treated as before. If the SF is < 200 µg/l, they will be monitored for a number of months to see if their iron levels increase and, if the iron levels increase, they will be treated for HHC, otherwise they will be discharged. If the SF is between 200 and 300 µg/l they will receive a DNA test. Those

TABLE 23 *Base-case results for the family testing decision tree for male siblings, per 100 people tested*

	Cases detected, *n*	Cases treated, *n*	Monitor, *n*	DNA test, *n*	Total cost, £	Additional cost/person tested, £	Additional cost/ case detected, £
Biochemical	19.0	19.7	86.2	0.0	23,628		
DNA testing	19.0	19.1	11.9	100.0	27,423	37.95	200

with a positive DNA test will be treated and those with a negative DNA test will be monitored. This scenario is very similar to the baseline biochemical test strategy because there are few people with a SF between 200 and 300 µg/l; it cost an extra £3 per case detected compared with the baseline biochemical test strategy.

The parameters in the family testing decision tree for male siblings were varied in sensitivity analyses and the results are shown in *Table 24*. The sensitivity analyses show that the conclusions from the decision tree are robust across all reasonable parameter ranges, i.e. the DNA strategy is more expensive than the baseline biochemical strategy. The most sensitive parameters were the cost of the DNA test and the specificity of the TS test. Results were also estimated for cost per person tested, and show that the additional cost per person tested varied between £18 and £58 for changes in the price of the DNA test.

A sensitivity analysis was run for women of 45 years of age with a threshold for SF of 200 µg/l and a penetrance of 0.32%.[60] In this case there were eight cases detected and an additional cost per case detected for the DNA strategy of £436 compared with the biochemical strategy.

Offspring

Table 25 shows the results from the family testing decision tree model for offspring of 25 years of age (*Figure 3*). The biochemical strategy tests all offspring with biochemical tests whereas the alternative strategy uses DNA tests. The DNA test strategy is cheaper than the baseline biochemical testing strategy and there are a similar number of HHC cases detected using both strategies. In the biochemical test strategy there are many more people monitored than in the DNA strategy. In this case, people are monitored five times, once every 5 years, and thus the monitoring cost is higher than the DNA test cost and so there is a cost saving for using DNA tests. These results assumed that 20% of offspring with HHC showed manifestations of the disease at the time of testing. The results are not very sensitive to this assumption.

The parameters in the family testing decision tree for offspring were varied in sensitivity analyses and the results are shown in *Table 26* and *Figure 6*. The sensitivity analyses show that the conclusions from the decision tree are valid across all reasonable parameter ranges, i.e. the DNA strategy is cost saving compared with the baseline strategy. The most sensitive parameters were the number of times that the offspring are monitored and the penetrance of HHC. Results were also estimated for cost per person tested and show that the cost saved per person tested varied between £139 and £423 for changes in the frequency of monitoring.

A sensitivity analysis was run for women of age 45 years with a threshold for SF of 200 µg/l and a

TABLE 24 *Sensitivity analyses for the family testing decision tree for male siblings*

		Inputs		Additional cost per case detected, £		
Variable	**Base case**	**Low[a]**	**High[a]**	**Low[a]**	**High[a]**	**Range**
Cost of DNA test, £	100	80	120	94	305	211
Cost of monitoring, £	71.15	56.92	85.38	256	144	112
Penetrance, %	76	60	93	253	163	90
TS specificity, %	94	75	99	149	211	62
SF specificity, %	85	75	99	189	215	26

SF, serum ferritin; TS, transferrin saturation.
a Results in the 'low' and 'high' columns use inputs from corresponding columns to give range; base-case results are shown in *Table 23*.

TABLE 25 *Base-case results for the family testing decision tree for offspring, per 100 people tested*

	Cases detected, *n*	Cases treated, *n*	Monitor, *n*	DNA test, *n*	Total cost, £	Cost saved/ person tested, £	Cost saved/case detected, £
Biochemical	3.5	4.4	98.6	0.0	46,753		
DNA testing	3.5	3.6	4.4	100.0	18,638	281.15	7982

TABLE 26 *Sensitivity analyses for the family testing decision tree for offspring*

		Inputs		Cost saved per case detected, £		
Variable	**Base case**	**Low[a]**	**High[a]**	**Low[a]**	**High[a]**	**Range**
Number of monitorings	5	3	7	4144	11,786	7642
Penetrance, %	76	60	93	10,111	6523	3588
TS specificity, %	94	75	99	9867	7430	2437
Cost of DNA test, £	100	80	120	8550	7415	1135
SF specificity, %	85	75	99	8406	7365	1041
Cost of monitoring, £	71.15	56.92	85.38	8366	7599	767
Initial proportion with iron overload	0.2	0	0.5	8141	7756	385

a Results in the 'low' and 'high' columns use inputs from corresponding columns to give range; base-case results are shown in *Table 25*.

penetrance of 0.32%.[60] In this case, there were 1.5 cases detected and a cost saved per case detected for the DNA strategy of £18,958.

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA)[112] was conducted to investigate the uncertainty of the model. The probability distributions were fitted to each of the model parameters using the high and low values from the sensitivity analysis and are shown in Appendix 11. The model used Monte Carlo simulation to randomly sample values for the model inputs and was run for 1000 iterations. In the PSA the cost saved per case detected for the diagnostic pathways varied between £97 and £187 for the 25th and 75th percentiles respectively. For the family testing decision tree the cost saved per case detected varied between £7323 and £9458 for offspring for the 25th and 75th percentiles respectively. For siblings the extra cost per case detected varied between £234 and £145 for the

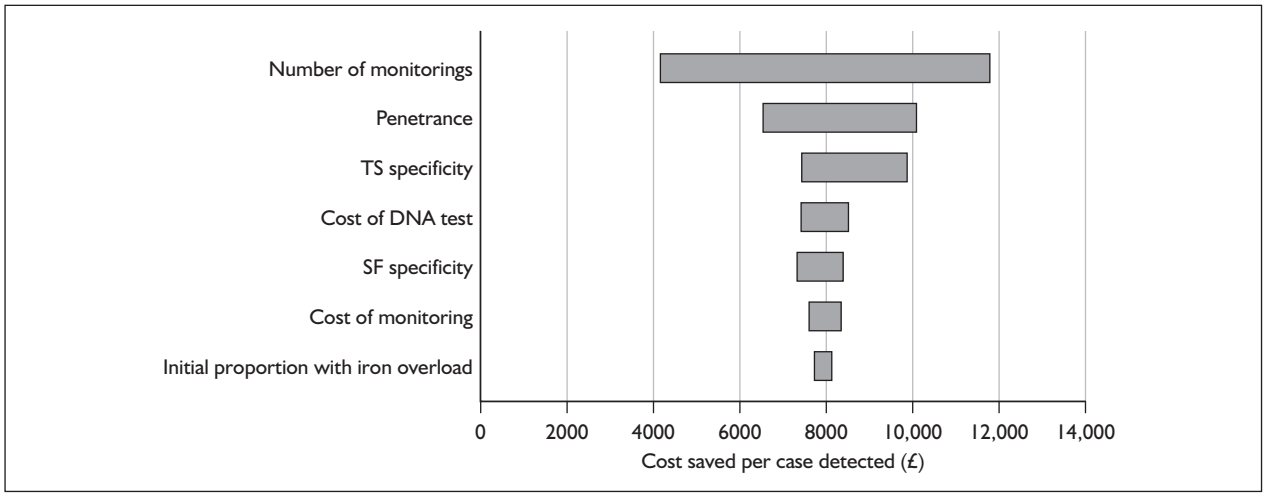

FIGURE 6 *Tornado plot of sensitivity analyses for family testing decision tree for offspring.*

25th and 75th percentiles respectively. More results are shown in Appendix 11.

Summary of results

Systematic review of economic evaluations

- Two studies were identified that met the inclusion criteria for the review.
- One study estimated the cost-effectiveness of screening for HHC in family members using genetic tests compared with a phenotypic test and no screening using a cost–utility model.
- The other study investigated the likely cost of genotyping spouses using a cost-minimisation model and whether this would reduce the number of investigations of children.
- Both studies were of reasonable quality when assessed against standard criteria, but as both studies were conducted in North America their generalisability to the UK is not clear.
- Gene testing was found to be a cost-effective method of screening relatives of patients with HHC in one study.
- In the other study genotyping the spouse of a homozygote was found to be the most cost-efficient strategy in family testing because it leads to more selective investigation of children for the *HFE* gene.

De novo model (SHTAC model)

Diagnostic strategies in people suspected of having haemochromatosis

- The DNA strategy is cost saving (because of the reduction in the number of liver biopsies performed).
- The sensitivity analyses show that the conclusion that the DNA strategy is cost saving is robust across all reasonable parameter ranges.
- The results were most sensitive to the specificity of the TS test, the cost of the liver biopsy test and the proportion of people with a positive DNA test for the C282Y mutation with raised SF.
- The cost saved per case detected varied between £62 and £184 for changes in the cost of the liver biopsy.

Family testing strategies (siblings)

- The DNA strategy is not cost saving (because of the extra costs of the DNA test). If the cost of the DNA test were to fall from £100 to £60, the DNA strategy would be the cheaper one.
- The sensitivity analyses show that the conclusion that the DNA strategy is more expensive is robust across all reasonable parameter ranges.
- The most sensitive parameters were the cost of the DNA test and the specificity of the TS test.
- The additional cost per case detected varied between £94 and £305 for changes in the price of the DNA test.

Family testing strategies (offspring)

- The DNA test strategy is cheaper than the baseline biochemical testing strategy.
- The sensitivity analyses show that the conclusions from the decision tree are valid across all reasonable parameter ranges.
- The most sensitive parameters were the number of times that the offspring are monitored and the penetrance of HHC.
- The cost saved per case detected varied between £4144 and £11,786 for changes in the frequency of monitoring.

Chapter 8
Discussion

Statement of principal findings

Clinical validity

Eleven studies were identified that could be used to estimate the clinical validity of genotyping for the C282Y mutation for the diagnosis of HHC. The quality of the studies using the criteria developed for this review was variable and the studies used a range of definitions for the clinical phenotype. The clinical sensitivity of C282Y homozygosity for HHC ranged from 28.4% to 100% in the 11 studies. When using only the studies most likely to have correctly defined haemochromatosis, which reported ruling out other causes of iron overload and related patients and which included the most northerly populations, sensitivity ranged from 91.3% to 92.4%. Clinical specificity ranged from 98.8% to 100%.

Clinical utility

No clinical effectiveness studies meeting the inclusion criteria for the review were identified. Two cost-effectiveness studies were identified. One study estimated the cost-effectiveness of screening for HHC in family members using genetic tests compared with phenotypic tests and no screening using a cost–utility model. The other study investigated the likely cost of genotyping spouses using a cost-minimisation model. Both studies were of reasonable quality when assessed against standard criteria, but as they were conducted in North America their generalisability to the UK is not clear. Gene testing was found to be a cost-effective method of screening relatives of patients with HHC. Genotyping the spouse of a homozygote was the most cost-efficient strategy in family testing because it leads to more selective investigation of children for the *HFE* gene.

Psychosocial aspects of DNA testing

Three cohort studies met the inclusion criteria for the review. Each study assessed and reported on the psychosocial outcomes of genetic testing for *HFE* in a different way. All of the studies had methodological limitations and the generalisability of these studies is difficult to determine. Generally the results suggest that genetic testing in the case of haemochromatosis is well accepted, is accompanied by few negative psychosocial outcomes and may lead to reduced anxiety. Control subjects in the one study that had a control group anticipated greater anxiety, depression, anger and difficulty in affording the genetic test than was reported by patients. In one study, clinically affected participants had significantly lower health-related quality of life as measured by the SF-36 PCS before genetic testing than unaffected participants, but this was no longer significantly different at 12 months post consultation. Another study reported significant improvements in the vitality subscale of the SF-36 and the PCS after participants were informed of their genetic test result. For generalised anxiety scores or intrusive thoughts, one study reported no statistically significant differences between clinically affected and clinically unaffected participants before and after genetic testing; another study reported that anxiety fell significantly in C282Y homozygotes and heterozygotes once they received their genetic testing results.

Economic evaluation

The de novo economic model found that for people suspected of having haemochromatosis the DNA strategy is cost saving compared with the baseline strategy (cost saved per case detected £123). This is because the cost savings that result from the reduced number of liver biopsies being performed are greater than the increased costs of monitoring. For family testing the DNA strategy is not cost saving in the case of testing siblings as the DNA test costs are higher than the reduced monitoring costs (additional cost per case detected £200). If the cost of the DNA test were to fall from £100 to £60, the DNA strategy would be the cheaper one. For family testing in the case of offspring of people with haemochromatosis, the DNA test strategy is cheaper than the baseline biochemical testing strategy (cost saved per case detected £7982). Sensitivity analyses show that the conclusions in each case are robust across all reasonable parameter values.

Strengths and limitations of the assessment

The review has certain strengths:

- It is independent of any vested interest.
- The review brings together the evidence for the clinical validity, clinical utility and psychosocial aspects of DNA testing for haemochromatosis following recommendations for evaluating a genetic test and applying consistent methods of critical appraisal, presentation and transparency. In addition, a de novo economic model has been developed following recognised guidelines.
- The review was guided by the principles for undertaking a systematic review. Before undertaking the review the methods were set out in a research protocol (Appendix 1) and this was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods employed to undertake the different stages of the review.
- An advisory group has informed the review from its initiation up to the development of the research protocol and completion of the report.
- Systematic searches were undertaken to identify data for the economic model and the main results summarised and presented.
- The quality of the clinical validity studies was assessed by criteria developed for the review, which combined relevant criteria from existing quality assessment tools.

In contrast, there were certain limitations placed upon the review:

- The number and type of studies available for inclusion in the review were limited. No RCTs were identified.
- Synthesis of the included studies was through narrative review. Because of the limitations of the literature, meta-analysis was deemed not appropriate.
- The economic evaluation was limited to a cost-minimisation study because of the lack of available information on the natural history and prognosis of haemochromatosis and associated quality of life issues.

Other relevant factors

General

- As mentioned in Chapter 3 the method used to evaluate DNA testing for HHC was largely based on the ACCE model developed by the Office of Genomics and Disease Prevention (Center for Disease Control, Atlanta, USA) and consists of systematic reviews of clinical validity, clinical utility and psychosocial aspects, with the development of a de novo economic model. The literature on the use of DNA testing for haemochromatosis is extensive; however, studies mostly consider gene frequencies in different populations, phenotypic and genotypic associations/correlations and population screening. The type of study employed is not always obvious from the title and abstract of publications. Finding studies that could be used for the different elements of the review was problematic, particularly for assessing the clinical validity of a genetic test. As such, a pragmatic approach was taken by developing different inclusion criteria for the different systematic reviews to ensure that relevant information was identified whilst retaining the focus of the review and allowing manageable synthesis of evidence.

Clinical validity

- The traditional diagnostic test assessment study that estimates the clinical sensitivity and clinical specificity of a test requires the new test to be compared with a reference standard (gold standard). However, this does not apply in the case of genetic tests for which the gold standard entails gene sequencing to detect mutations.[113] Potential alternative gold standards in the case of haemochromatosis are no longer used for diagnostic purposes, such as liver biopsy, which is used mostly for prognosis, and haplotyping, which has been superseded since the discovery of the *HFE* gene. As such, traditional diagnostic test assessment studies are inappropriate and are not available or applicable in this case.
- The ideal way to assess the clinical validity of DNA testing for haemochromatosis would be to follow a large group of individuals through to expression of phenotypic disease and perform genetic testing. No such population-based cohort studies are available and such studies could be considered unethical and are therefore unlikely. As such, clinical validity has been assessed here by considering studies that identify a group of individuals who have the primary iron overload phenotype and then determining the proportion who are C282Y homozygous and by comparing them with a control group. The control subjects are individuals who do not have the phenotype

of interest according to the disease case definition.[114] It is only through the use of such control subjects that an assessment of specificity can be made. The use of such studies has limitations though in that individuals in the control group who test positive may yet go on to develop the phenotypic disease. Although this risk is likely to be small because of the prevalence and penetrance of HHC, it must be acknowledged that calculation of the specificity of the genetic mutation (C282Y) for HHC from such studies may not be accurate. Specificity of 100% for the homozygous C282Y mutation in patients with phenotypic expression has been reported.[115]

- Studies that find the percentage of individuals who have the primary iron overload phenotype and who have a positive test result for C282Y homozygosity to give the clinical sensitivity of the mutation are in effect gene frequency studies. As such, there is some overlap between the epidemiology studies and those included in the clinical validity section.
- An associated difficulty in the case of HHC is specifying the exact diagnostic criteria or reference standard used to define the condition. The disease may sometimes be defined phenotypically by the presence of certain signs and symptoms and at other times genotypically by reference to the mutations that give rise to the disease. It has been suggested that the definition of a genetic disease should require both the clinical manifestations and the presence of the mutation; however, it has also been suggested that the presence of either the clinical features or the mutation suffices for a definitive diagnosis. In assessing genetic testing, as in the case of haemochromatosis, the definition of the disease should be by reference to signs and symptoms or clinical features but not by reference to genotype.[114] The definition of cases may vary from signs and symptoms to confirmed iron overload with clinical manifestations and this can affect the characteristics of the genetic test and the reported clinical validity (see below).
- Clinical sensitivity from the included studies ranges from 28% to 100%. It can be seen from these results that the reliability of estimating clinical sensitivity of C282Y homozygosity for HHC is particularly susceptible to the definition of the clinical phenotype used in the studies. When the definition is more rigorous and strict criteria for phenotypic expression are used, the clinical sensitivity increases.
- There are also difficulties associated with assessing a prognostic or predictive test when the genotype is more highly prevalent than the phenotype. In classic rare single gene disorders the genotype is an accurate predictor of the phenotype because both genotype and phenotype are sufficiently rare that if they occur together the predictive value is high. This is not the case for haemochromatosis and will not be the case for the other common complex genetic diseases.
- Quality issues of diagnostic test studies are different from those in effectiveness studies and the quality assessment of clinical validity studies in the context of DNA are even further removed from the usual issues. Therefore, as the clinical validity studies did not conform to typical diagnostic accuracy studies or observational studies, a modified Spitzer assessment tool, incorporating elements from QUADAS, was used, which concentrated on the issues of particular relevance to the studies in question. That is, aspects considered for quality assessment included whether there was adequate description of the haemochromatosis group of patients; the likelihood that the definition of disease was an accurate reflection of the disease and that the patients were a representative sample; whether the control population was adequately described and appropriate; whether the groups were comparable in terms of factors such as age, sex and ancestry; whether the DNA tests were adequately described and appropriate; whether outcomes were fully reported; whether there was mention of missing data; and the generalisablity of results.

Clinical utility

- The best evidence for the clinical utility of a diagnostic test is an RCT with patients randomly assigned to alternative diagnostic strategies with clinical or cost-effectiveness reported.[85] In the absence of RCTs it was intended to assess the clinical effectiveness of DNA testing by using the highest level of evidence available that considered suspected cases of HHC (or relatives of cases) and comparative testing strategies and reported patient-based outcomes. No such studies with appropriate designs and outcomes were found. Some studies that purported to be clinical utility studies were problematic in that they reported gene frequency without any clinical or cost-effectiveness measure. Another example of difficulties associated with the literature was that some studies which initially appeared to be comparing diagnostic strategies in fact

compared different groups of patients using biochemical and DNA testing algorithms rather than suspected HHC patients tested by different diagnostic algorithms with or without DNA tests to assess the utility of DNA testing.
- Two cost-effectiveness studies were identified. Although these were conducted in North America and used different approaches from that used in the current project, they support the case that incorporating DNA testing in diagnostic algorithms is likely to be a cost-saving strategy.

Psychosocial aspects

- The aims of the psychosocial section of the review were very specific: to compare the psychosocial benefits and harms of adding DNA testing to diagnostic algorithms. However, there were few studies that could be included in the review. An ideal study might have randomised people with suspected HHC and first-degree relatives into a trial in which participants in one arm received standard biochemical tests to diagnose HHC and those in the second arm received DNA testing in addition to the standard biochemical tests. With data collection on psychosocial outcomes carried out both before and after the intervention and disclosure of test results, such a study could provide an indication of whether the prospect of DNA testing for HHC is any more stressful than that of biochemical testing. Additionally, such a study might also indicate whether receiving DNA test results has a greater positive or negative psychosocial impact than receiving biochemical test results. Longer-term follow-up would be essential to capture data for outcomes such as treatment compliance, discrimination and stigmatisation.
- The three studies included in this report took place in the USA, Canada and Australia and therefore it is important to consider the nature of the health-care systems in these countries as this might impact on the transferability of the results to the UK setting. In the USA patients must either have health insurance or pay for their medical care directly themselves. Therefore, in the USA people might be expected to have more worries about financial and insurance issues in relation to a diagnosis of haemochromatosis than those in Canada and Australia, which have publicly funded health insurance plans, or those in the UK, where health care is provided by the NHS.
- The three included cohort studies employed different methods and reported results in different ways, which made it difficult to synthesise the evidence and draw any firm conclusions from the review. Nevertheless a common theme emerges. After people were informed of their test results anxiety levels fell or remained at pretest result levels and this was mirrored in the results for general health-related quality of life, which either improved in some aspects or stayed constant with respect to pretest result values. This suggests that when the genetic test result confirms a diagnosis of HHC this does not have a negative impact in terms of anxiety or health-related quality of life, and indeed there is some evidence to suggest that once the test result is received anxiety levels may fall and health-related quality of life can improve.
- A second common theme that emerges from two of the included studies is that most patients are able to correctly recall the information that they have been given about haemochromatosis. However, there were areas in which recall and/or understanding were poor, for example understanding the difference between *HFE* genotyping and the TS test result, and knowing that the C282Y mutation is found in most people with haemochromatosis. Of particular potential concern is the finding in one study that 34% of participants did not recall having received a genetic test result, and in the second study that between 16% and 21% of homozygotes, heterozygotes and compound heterozygotes were unable to remember their mutation status. This highlights the importance of comprehensive pretest and post-test counselling to ensure that patients fully understand the test results that they receive.
- The limited evidence base in this area does not address whether there might be different psychosocial effects of testing, depending on whether an individual is referred for genetic testing because they have signs and symptoms suggestive of HHC or whether they are asymptomatic and have been referred for testing following diagnosis of HHC in a family member.
- Population screening studies were not included in this review and a comprehensive search for such studies was not undertaken. However, those population screening studies that were excluded from this review (listed in Appendix 3) report findings that are similar to those reported here. For instance, when phenotypic and genotypic screening strategies have been compared, both have been acceptable[79,116] and little psychological disturbance has been apparent in the short term with

either strategy.[78,117] Negative psychosocial consequences have been reported to be rare.[118]
- Although the evidence shows that there are not likely to be detrimental psychological effects of genetic testing it has been suggested that patients would benefit from routine assessment of psychological distress and that referral to a mental health professional should be available for those whose levels suggest a need for clinical intervention.[97]

Economic evaluation

Diagnostic strategies in people suspected of having haemochromatosis

- The analysis in this report shows that, in people suspected of having HHC, DNA testing is cost saving compared with testing using liver biopsy. The analysis did not consider complications from liver biopsy, such as bleeding. Gilmore and colleagues[119] estimated a death rate of 0.13–0.33% and a bleeding rate requiring transfusion of 0.7% for people who have ultrasound-guided liver biopsy. These rates are for a different patient group with a higher risk of haemorrhage and as such were not used in the analysis. However, they do suggest that had complications been included results would have been even more favourable towards the DNA testing strategy. In the DNA testing strategy there were less than half the number of liver biopsies performed than in the liver biopsy testing strategy and so there will be a similar reduction in liver biopsy complications.
- The sensitivity analyses show that the conclusions are unlikely to change, even with better data. There is some uncertainty about the prevalence of HHC in people presenting with symptoms of haemochromatosis. The data used in the model were taken from a study of a liver clinic in south London and may not be exactly representative of those with symptoms of HHC. However, the cost saved per case detected varied little when the prevalence was doubled or halved. Furthermore, the DNA test strategy remains cost saving for all possible values of prevalence.
- The results were most sensitive to the specificity of the TS test, the cost of the liver biopsy test and the proportion of people with a positive DNA test for C282Y homozygosity and raised SF. The cost saved per case detected varied between £62 and £184 for changes in the cost of the liver biopsy.
- The results were reported as cost per case detected as this was deemed of most relevance to the NHS and clinicians. Cost saved per person tested for HHC was also investigated. These outcomes may produce results that are sensitive to the outcome measure used and there is a possibility that some results may be misleading. For example, the cost per case detected is affected by the number of cases detected (i.e. the sensitivity of the test). However, the sensitivity analyses showed similar results for cost saved per person tested as for cost per case detected except that the results for cost saved per person tested are not sensitive to TS specificity.
- The decision tree model does not consider long-term costs and consequences of HHC. This is because the data on the long-term costs and consequences was considered of poor quality. Furthermore, the analyses in this project detected the same number of cases of HHC using both strategies and so a cost-minimisation model is more appropriate.

Family testing strategies (siblings)

- This analysis shows that DNA testing is not a cost-saving strategy compared with testing using biochemical tests for screening siblings of a patient with HHC. However, if the cost of the DNA test were to reduce from £100 to £60 the DNA strategy would be the cheaper one. Also, the model does not estimate the likely inconvenience and anxiety attached to monitoring and treating patients without HHC. As the DNA strategy monitored significantly fewer and treated fewer patients who did not have HHC than the biochemical strategy this could impact on the long-term cost-effectiveness of DNA testing in siblings.
- The sensitivity analyses show that the conclusions are unlikely to change, even with better data. There is some uncertainty about the penetrance of HHC for people with the HHC genotype; however, the cost per case detected varied little when the penetrance was changed. Furthermore the DNA test strategy remains more costly for all possible values of penetrance. The most sensitive parameters were the costs of the DNA test and monitoring. The additional cost per case detected varied between £94 and £305 for changes in the price of the DNA test.
- The additional cost per person tested was also investigated and shows similar results, varying between £18 and £58 for changes in the price of the DNA test.
- A strategy of not screening relatives of patients with HHC would require comparing the long-term costs and consequences of HHC and

was not considered for the reasons discussed above. Previous studies have reported the appropriateness of screening first-degree relatives of affected patients.[11,99] El-Serag and colleagues[99] calculated the cost of screening a pedigree that consists of up to three siblings and found that the screening of family members was dominant for all screening strategies compared with no screening. In contrast to the results in this paper they found that screening with serum iron studies was more expensive than gene testing although it is unclear why from the results reported.

Family testing strategies (offspring)

- This analysis shows that DNA testing is a cost-saving strategy compared with testing using biochemical tests for screening offspring of a patient with HHC. The DNA strategy monitored significantly fewer patients and treated fewer patients who did not have HHC than the biochemical strategy. With the biochemical testing strategy most children of probands would have to undergo repeated testing until they reached 40 years of age. In the DNA test strategy 95% of these children will avoid further unnecessary investigations and the associated potential long-term uncertainty and anxiety.
- As for the other decision tree models the sensitivity analyses show that these conclusions are unlikely to change, even with better data. The most sensitive parameters were the number of times that the offspring are monitored and the penetrance of HHC. The cost saved per case detected varied between £4144 and £11,786 for changes in the frequency of monitoring.
- The cost saved per person tested varied between £139 and £423 for changes in the frequency of monitoring.
- The model developed here did not include a strategy for testing the spouse first before testing the offspring. Adams[100] recommended this strategy to avoid unnecessary investigation of offspring of probands. El-Serag and colleagues[99] found that testing the spouse before children was the most cost-effective strategy when testing two or more children. The current fertility rate in the UK is 1.8 liveborn children per woman and so such analyses are of limited relevance to the UK. Also, these previous analyses do not take into account the effect of identifying carriers of the gene and what further investigations might be required. The purpose of testing within families is to identify cases that might require treatment and those that will not. Testing spouses rather than directly testing the individual at-risk children is merging into population screening for haemochromatosis, which is not supported by evidence of effectiveness. An additional concern is the information and counselling requirements of those tested. Although there is little evidence that genetic testing for susceptibility to haemochromatosis leads to long-term adverse psychosocial consequences, mild negative effects on participants with indeterminate results from screening programmes have been noted.[120] For these reasons the family testing strategy evaluated in the current project was to test the offspring directly.

Genetic exceptionalism and phenotype versus genotype

- It is sometimes argued that information derived from a genetic source has special properties over that derived from a phenotypic source. If this were the case it could be argued that the identification of genetic susceptibility in haemochromatosis – the 'at-risk genotype' – has different properties to the identification of the iron overload state by phenotypic means. However, the diagnosis of haemochromatosis is made by combining the genetic information with the phenotypic information. It is suggested that for clinical purposes the case definition should be homozygosity for the common C282Y mutation with a raised SF. The person with homozygosity and normal iron studies is at risk of developing *HFE*-related iron overload but does not have haemochromatosis. The person who is a compound heterozygote with raised SF with no other explanation could be regarded as having *HFE*-related haemochromatosis. There will be a small group of patients who have iron overload with no other explanation who are negative for the common mutations in the *HFE* gene. These may be classified as atypical haemochromatosis and in a routine clinical setting further genetic analysis is impractical. Using this combination of genotypic and phenotypic information is probably the best scenario for clinical decision-making but does of course make it difficult to conduct classic studies comparing genotype and phenotype.[121]
- The special properties of information derived from DNA-based analysis are said to relate to issues such as concern for kin, potential for discrimination and stigmatisation, the potential for long-term storage and ease of access to

samples for future analysis, and predictive value. However, all of these characteristics can be applied to medical and health information derived from non-genetic sources. More careful analysis suggests that it is not the method by which the information is derived that gives it special status but the context in which that information is used.[76] In the case of haemochromatosis, as outlined above, the clinical definition relies on both genotypic and phenotypic information. The context of the information is what defines the property of that information, not how it is derived. The results of the genetic analysis can be used to diagnose those who might benefit from treatment, to predict those at risk of developing iron overload and to rule it out in those not at risk.

Chapter 9
Conclusions

DNA testing for haemochromatosis

The results suggest that using a diagnostic strategy that incorporates DNA testing is cost saving in case identification and testing of offspring of patients with haemochromatosis. The results for siblings are more surprising in that they suggest that DNA testing is not cost saving (because of DNA test costs being higher than the reduced monitoring costs). However, in this study, which considered cost per case detected, it was not possible to factor in the benefit of reassurance and reduction in anxiety resulting from DNA testing, which could be expected to have an impact on the long-term cost-effectiveness of DNA testing in siblings.

As such, the preferred strategy in practice would be using DNA testing for case identification and for both offspring and siblings of patients with haemochromatosis as this can result in reduced anxiety with no adverse effects.

Implications for service provision

The conclusions drawn from this study suggest that DNA testing should be used in conjunction with testing iron parameters when there is a clear clinical indication of suspicion of being at risk for haemochromatosis because of biochemical criteria or when being at familial risk for haemochromatosis. Although clinical practice amongst those expert and interested in the management of the condition is already thought to follow this strategy, the development and dissemination of guidelines to physicians in both primary and secondary care is advisable.

There are implications for service delivery in that cost volume issues could reduce the cost of DNA testing through a molecular genetic laboratory network, which could rationalise the use of resources. Access to genetic testing and centralisation of test provision in expert laboratories in line with the Carter report[122] would lower the cost of testing, improve the cost-effectiveness of the strategy and improve the quality of information provided to clinicians and patients.

Suggested research priorities

It is apparent from this project that the evidence base for assessing the use of DNA testing for haemochromatosis is limited in quality and in quantity and that further primary research in the form of prospective long-term follow-up studies is required. However, the need for research must be tempered by the scale of the problem, which involves an inexpensive test, and the uncertainty around the added value of such costly research.

An area of research more likely to be of practical value is epidemiological research into the factors, both other genetic factors and environmental factors, that affect the penetrance of the genetic mutation, to identify those people homozygous for the mutation who are likely to develop iron overload. Use could be made of databases, such as the UK Biobank, for case–control studies based on the accurate phenotype of proven haemochromatosis cases and a large control population.

It is unlikely that further research into the psychosocial aspects of the use of DNA testing for haemochromatosis will be required as research has shown that such testing reduces anxiety and because treatment is simple and effective. However, this could change if other factors that influence the expression of the phenotype were identified.

Acknowledgements

Various people, including members of the advisory group, contributed to the project and we are grateful for their help: Valerie Hadfield, Director of the Haemochromatosis Society; Elizabeth Hodson, Information Assistant, WIHRD, University of Southampton; Alison Price, Information Scientist, WIHRD, University of Southampton; James Raftery, Professor of Health Technology Assessment, University of Southampton; Simon Sanderson, Consultant in Public Health Medicine, Public Health Genetics Unit, Cambridge; Kim Wherry, Finance Officer, WIHRD, University of Southampton.

Contribution of authors

J Bryant (Senior Research Fellow, SHTAC) developed the research protocol, assisted in the development of the search strategy, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, assisted in the development of the economic evaluation, drafted and edited the final report and project managed the study. K Cooper (Research Fellow, SHTAC) developed the research protocol, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, developed the economic evaluation and drafted the report. J Picot (Research Fellow, SHTAC) developed the research protocol, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, assisted in the development of the economic evaluation and drafted the report. A Clegg (Professor in Health Service Research, Director of SHTAC), joint principal investigator, developed the research protocol, assisted in the development of the search strategy, assessed studies for inclusion, quality assessed included studies, assisted in the development of the economic evaluation and drafted the report. P Roderick (Reader, Director of Public Health Sciences and Medical Statistics, University of Southampton) developed the research protocol, assisted in the development of the search strategy, assisted in the development of the economic evaluation and drafted the report. W Rosenberg (Professor of Hepatology, University of Southampton) assisted in development of the research protocol and assisted in the development of the economic evaluation. C Patch (Consultant Genetic Counsellor, Guy's and St Thomas' NHS Foundation Trust), joint principal investigator, obtained the original funding, developed the research protocol, assisted in the development of the search strategy, assessed studies for inclusion, extracted data and quality assessed included studies, assisted in the development of the economic evaluation and drafted the report.

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Accepted for publication

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Appendix 1

Review methods from the research protocol

Methods for reviewing effectiveness

The a priori methods used for the review are outlined in the following sections. The sources of information used are outlined in Appendix 2.

Inclusion and exclusion criteria

Specific inclusion criteria will be defined and tailored to each of the systematic reviews and systematic searches undertaken.

The planned inclusion/exclusion criteria for the systematic reviews are shown in *Table 27*.

In addition, the results of systematic literature searches to identify relevant studies in the areas of the epidemiology of haemochromatosis, performance of biochemical tests and complications of liver biopsy will be assessed against inclusion criteria and used to inform the decision models (*Table 28*).

The full literature search results will be screened by one reviewer and checked by a second reviewer to identify all citations that may meet the inclusion criteria. Full manuscripts of all selected citations will be retrieved and assessed by two reviewers

TABLE 27 *Inclusion criteria for systematic reviews*

	Systematic review: clinical validity	Systematic review: clinical utility		Systematic review: psychosocial aspects of DNA testing
	DNA tests	**Clinical effectiveness of diagnostic strategies**	**Cost-effectiveness of diagnostic strategies**	
Patients	Caucasian patients with iron overload, signs and symptoms suggestive of HHC (defined) Emphasis to be UK populations/north European	Caucasian patients with iron overload, signs and symptoms suggestive of HHC (defined) Relatives of suspected cases Exclude specialist clinic-based patient groups (e.g. diabetic clinics) and population screening	Caucasian patients with iron overload, signs and symptoms suggestive of HHC (defined) Relatives of suspected cases Exclude specialist clinic-based patient groups (e.g. diabetic clinics) and population screening	At-risk individuals, i.e. suspected HHC cases and first-degree relatives
Intervention	DNA tests	DNA tests	DNA tests	DNA tests
Comparator	Control population (e.g. healthy control subjects or comparator patient group attending clinic/hospital for non-HHC/iron overload reasons)	Any case identification strategy. May include liver biopsy to give HII or quantitative phlebotomy or other iron studies	Any case identification strategy. May include liver biopsy to give HII or quantitative phlebotomy or other iron studies	n/a
Outcomes	Sensitivity and specificity (reported or calculable)	Treatment, morbidity, mortality, QoL, psychosocial (patient-based outcomes)	Cost per case detected, cost-minimisation, cost-effectiveness or cost–utility	Psychosocial (treatment compliance, psychological, legal implications, QoL, discrimination/ stigmatisation)
Design	Controlled cohort or case–control	RCTs, controlled cohort, case–control (highest level of evidence only)	Economic evaluations, modelling studies	Any primary research; quantitative and qualitative

HII, hepatic iron index; n/a, not applicable; QoL, quality of life; RCT, randomised controlled trial.

TABLE 28 *Inclusion criteria for systematic searches*

	Epidemiology	Biochemical tests	Complications of liver biopsy
Patients	Caucasian patients with iron overload, signs and symptoms suggestive of HHC (defined) Relatives of suspected cases Emphasis to be UK populations/ north European	Caucasian patients with iron overload, signs and symptoms suggestive of HHC (defined)	Caucasian patients with iron overload, signs and symptoms suggestive of HHC (defined) If no data, extend to other patients having elective biopsy without decompensated liver disease
Intervention	n/a	Transferrin saturation and serum ferritin reporting cut-off values	Ultrasound-guided liver biopsy
Comparator	n/a	Liver biopsy to give HII or quantitative phlebotomy or DNA (to confirm diagnosis)	Liver biopsy without ultrasound
Outcomes	Incidence, prevalence, natural history, penetrance	Sensitivity and specificity, PPV and NPV; reported and/or calculable	Adverse events; complications reported as frequencies, probabilities
Design	Observational studies	RCTs, cohorts, case–control (highest level of evidence only)	RCTs

HII, hepatic iron index; NPV, negative predictive value; PPV, positive predictive index; RCT, randomised controlled trial.

against the inclusion criteria. An inclusion flow chart will be developed and used for each paper assessed. Disagreements over study inclusion will be resolved by consensus or if necessary by arbitration by a third reviewer.

Data extraction

The extraction of studies' findings will be conducted by two reviewers using a predesigned and piloted data extraction form to avoid any errors. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration by a third reviewer.

Quality assessment strategy

The methodological quality of included studies will be assessed using formal tools specific to the design of the study and focusing on possible sources of bias. Quality assessment of RCTs will be conducted using criteria developed by the NHS Centre for Reviews and Dissemination[123] and observational studies will be assessed using criteria developed by Spitzer and colleagues.[81] For diagnostic test studies quality assessment will be conducted using a tool such as the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) where appropriate.[80] Quality assessment of economic evaluations will be conducted using a checklist adapted from those developed by Drummond and Jefferson[82] and Philips and colleagues.[83] Study quality will be assessed by two reviewers. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration involving a third reviewer.

Methods of analysis/synthesis

The methods of data synthesis will be determined by the nature of the studies identified through searches and included in the review. Quantitative synthesis of results, for example meta-analysis, will be considered if there are several high-quality studies of the same design, and sources of heterogeneity will be investigated by subgroup analyses if applicable. The results of any included studies suitable for quantitative synthesis will also be summarised in a narrative form along with a narrative synthesis of the results from studies for which quantitative synthesis is not possible. All results will also be tabulated.

Evaluation of genetic tests

Various authors have raised issues concerning the methods for assessing diagnostic tests and there is a consensus that explicit frameworks should be developed analogous to those used in studies of clinical effectiveness.[84,85] The ACCE model has been developed by the Office of Genomics and Disease Prevention (Center for Disease Control, Atlanta, USA), working with the Foundation for Blood Research, to evaluate DNA-based genetic tests.[53] This model takes its name from the four components of the evaluation: *A*nalytic validity, *C*linical validity, *C*linical utility and associated *E*thical, legal and social issues. This model is still in

its development stage; however, it provides a useful framework to inform the evaluation of genetic tests.

Analytical validity is the ability of the test to accurately and reliably measure the genotype of interest and is concerned with assessing test performance in the laboratory and is closely related to quality assurance of the laboratory processes surrounding the test. Clinical validity is defined as the ability of the test to detect or predict the phenotype (disorder) of interest. Elements of clinical validity include clinical sensitivity, clinical specificity, and positive and negative predictive values of the test (*Table 29*). The clinical sensitivity measures the proportion of individuals with the defined disorder, or who will get the disorder in the future, and whose test results are positive, whereas clinical specificity measures the proportion of individuals who do not have the defined clinical disorder and whose test results are negative.

Clinical utility is defined as the likelihood that the test will lead to an improved outcome, and incorporates assessment of the risk and benefits of genetic testing, as well as economic evaluation. This is perhaps the most important aspect of the evaluation in that it assesses whether testing will alter clinical management, benefit those tested and at what cost.

Of particular relevance to this project are questions of clinical validity and clinical utility. Additionally, the last component of the ACCE framework will be covered by considering psychosocial aspects of using genetic testing for HHC in terms of psychological issues, quality of life, discrimination and stigmatisation and legal implications.

Methods for economic evaluation

A comparison of the costs and consequences of the diagnostic testing strategies with and without DNA testing will be made using decision-analytic models. These will be populated with data from systematic reviews and systematic searches of the literature and, when necessary, using guidelines and expert opinion. Costs will be derived from primary data from previous studies and from national and local NHS unit costs. The outcome will be reported as cost per case detected.

The structure and data inputs of all of the decision trees will be informed by systematic literature reviews and the results of systematic searches and by discussion with experts.

TABLE 29 *Calculation of components of clinical validity*

	Participants		
Test	**With disease**	**Without disease**	**Total**
Positive	a	b	a+b
Negative	c	d	c+d
Total	a+c	b+d	a+b+c+d

Sensitivity = a/a+c.
Specificity = d/b+d.
Positive predictive value (PPV) = a/a+ b.
Negative predictive value (NPV) = d/c+d.
PPV and NPV vary with disease prevalence but are useful clinically for ruling the condition in or out.
The ideal study to determine these parameters in the case of HHC is a population-based genotyped cohort of young adults followed through life; as this is not possible, a pragmatic approach is to use controlled cohort studies.

Appendix 2

Sources of information, including databases searched and search terms

The following databases were searched for published studies and ongoing research. Searches were restricted to the English language and human studies. Bibliographies of related papers were assessed for relevant studies.

Databases searched	Issues or dates searched
Cochrane Library (Database of Systematic Reviews and Controlled Trials Register)	Issue 2, 19 April 2007
MEDLINE (Ovid)	1966–2007 (19 April 2007)
EMBASE (Ovid)	1980–2007 (19 April 2007)
ISI Proceedings	2003–7 (23 April 2007)
NHS Economic Evaluations Database (NHS CRD databases)	23 April 2007
NHS HTA database (NHS CRD databases)	23 April 2007
NHS DARE database (NHS CRD databases)	23 April 2007
ISI Science Citation Index	1970–2007 (23 April 2007)
BIOSIS Previews (EDINA) meeting abstracts	2003–7 (23 April 2007)
HuGeNeT	23 April 2007
EconLit	23 April 2007
MEDION	23 April 2007
National Guidelines Clearinghouse	23 April 2007
UK National Screening Committee	23 April 2007
PsycINFO (OVID)	1985–2007 (23 April 2007)
CINAHL (OVID)	1982–2007 (23 April 2007)
NRR (National Research Register)	23 April 2007

Search terms used for the diagnosis of haemochromatosis were as follows in MEDLINE (Ovid):

1. Hemochromatosis/
2. (HHC or HH).ti,ab.
3. Metal Metabolism, Inborn Errors/
4. (hemochromatosis or haemochromatosis).ti,ab.
5. (hemochromotosis or haemochromotosis).ti,ab.
6. (hemachromatosis or haemachromatosis).ti,ab.
7. 4 or 5 or 6
8. hereditary.ti,ab.
9. 7 and 8 (1328)
10. 1 or 2 or 3 or 9
11. Ferritin/an, bl, du [Analysis, Blood, Diagnostic Use]
12. Transferrin/an, du, bl
13. serum iron.ti,ab.
14. serum ferritin.ti,ab.
15. transferrin saturat$.ti,ab.
16. (iron adj3 (overload$or excess$or accumulat$or build?up or bind$)).ti,ab.
17. Iron Overload/di
18. ((biochem$or liver or blood) adj3 (test$or screen$or biopsy or detect$)).ti,ab.
19. Biopsy/
20. "Serologic Tests"/
21. Blood Chemical Analysis/
22. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. exp HLA Antigens/ge, an, bl, du [Genetics, Analysis, Blood, Diagnostic Use]
24. ((family or relat$or parent$or sibling$or mother$or father$or brother$or sister$) adj5 (screen$or test$or detect$or cascad$)).ti,ab.
25. 23 or 24
26. (HFE adj5 gene).ti,ab.
27. (C282Y or H63D).ti,ab.
28. ((DNA or genetic or gene) adj3 (test$or screen$or detect$)).ti,ab.
29. Homozygote/
30. Genetic Screening/
31. 26 or 27 or 28 or 29 or 30
32. limit 31 to yr="1996 – 2006"
33. 32 or 25
34. 22 or 33
35. "Sensitivity and Specificity"/
36. predictive value of tests/
37. false positive reactions/
38. False Negative Reactions/
39. ROC curve/
40. Diagnosis, Differential/
41. Reference Values/
42. (diagnos$adj3 (efficen$or efficac$or effectiv$or accuracy or correct or reliab$or error$or mistake$or inaccura$or incorrect or unreliable)).ti,ab.
43. (sensitivity adj3 (test or tests)).ti,ab.
44. (specificity adj3 (test or tests)).ti,ab.
45. (screen$or test$).mp.
46. ((detect$or identif$) and (C282Y or H63D or HLA-H)).ti,ab.
47. 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48. animal/
49. human/
50. 48 not (48 and 49)
51. 10 and 34 and 47
52. 51 not 50
53. limit 52 to english language

Search terms for psychosocial aspects were as follows in MEDLINE (Ovid):

1. Hemochromatosis/
2. (hemochromatosis or haemochromatosis).ti,ab.
3. (hemochromotosis or haemochromotosis).ti,ab.
4. (hemachromatosis or haemachromatosis).ti,ab.
5. 2 or 3 or 4
6. hereditary.ti,ab.
7. 5 and 6
8. 1 or 7
9. ((family or relat$or parent$or sibling$or mother$or father$or brother$or sister$) adj5 (screen$or test$or detect$or cascad$)).ti,ab.
10. (HFE adj5 gene).ti,ab.
11. (C282Y or H63D).ti,ab.
12. ((DNA or genetic or gene) adj3 (test$or screen$or detect$)).ti,ab.
13. Genetic Screening/
14. (screen$or test$).mp.
15. 10 or 11
16. 14 and 15
17. 9 or 12 or 13 or 14 or 16
18. exp Psychology/
19. psychosocial.mp.
20. "Patient Acceptance of Health Care"/
21. (accept$or fear$or worr$or perception or attitude$or concern$).ti,ab.
22. 18 or 19 or 20 or 21
23. 17 and 22 and 8
24. limit 23 to (humans and english language)

Search terms for epidemiological studies in MEDLINE (Ovid) were as follows:

1. (hemochromatosis or haemochromatosis).ti,ab.
2. (hemochromotosis or haemochromotosis).ti,ab.
3. (hemachromatosis or haemachromatosis).ti,ab.
4. 1 or 2 or 3
5. hereditary.ti,ab.

6. 4 and 5
7. Hemochromatosis/ep, et [Epidemiology, Etiology]
8. incidence.ti.
9. prevalence.ti.
10. *incidence/
11. *Prevalence/
12. *Risk Factors/
13. *Time Factors/
14. epidemiol.ti.
15. etiolog$.ti.
16. aetiolog$.ti.
17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 7 or 6
19. 17 and 18
20. limit 19 to (humans and english language)

Search terms for liver biopsy complications in MEDLINE (Ovid) were as follows:

1. Hemochromatosis/
2. Liver/
3. Biopsy/ae, mo, co
4. (1 or 2) and 3
5. (liver biopsy adj5 (complication$or adverse$or safety or death)).mp.
6. 4 or 5
7. limit 6 to (humans and english language)

Primary search terms for economic searches in MEDLINE (Ovid) were as follows:

1. Hemochromatosis/
2. (HHC or HH).ti,ab.
3. Metal Metabolism, Inborn Errors/
4. (hemochromatosis or haemochromatosis).ti,ab.
5. (hemochromotosis or haemochromotosis).ti,ab.
6. (hemachromatosis or haemachromatosis).ti,ab.
7. 4 or 5 or 6
8. hereditary.ti,ab.
9. 7 and 8
10. 1 or 2 or 3 or 9
55. exp ECONOMICS/
56. exp ECONOMICS, HOSPITAL/
57. exp ECONOMICS, PHARMACEUTICAL/
58. exp ECONOMICS, NURSING/
59. exp ECONOMICS, DENTAL/
60. exp ECONOMICS, MEDICAL/
61. exp "Costs and Cost Analysis"/
62. VALUE OF LIFE/
63. exp MODELS, ECONOMIC/
64. exp FEES/and CHARGES/
65. exp BUDGETS/
66. (economic$or price$or pricing or pharmacoeconomic$or pharma economic$).tw.
67. (cost$or costly or costing$or costed).tw.
68. (cost$adj2 (benefit$or utilit$or minim$)).tw.
69. (expenditure$not energy).tw.
70. (value adj2 (money or monetary)).tw.
71. budget$.tw.
72. (economic adj2 burden).tw.
73. "resource use".ti,ab.
74. or/55–73
75. letter.pt.
76. editorial.pt.
77. comment.pt.
78. or/75–77
79. 74 not 78
80. 10 and 79
81. limit 80 to (humans and english language)

The search strategies were translated to run in the databases listed above. Full search strategies are available upon request.

Appendix 3

List of excluded studies

Clinical validity and utility

Adams PC, Chakrabarti S. Genotypic/phenotypic correlations in genetic hemochromatosis: evolution of diagnostic criteria. *Gastroenterology* 1998;**114**:319–23. (Location Canada.)

Adams PC. Implications of genotyping of spouses to limit investigation of children in genetic hemochromatosis. *Clin Genet* 1998;**53**:176–8. (Location Canada: included under cost-effectiveness studies.)

Adams PC, Kertesz AE, McLaren CE, Barr R, Bamford A, Chakrabarti S. Population screening for hemochromatosis: a comparison of unbound iron-binding capacity, transferrin saturation, and C282Y genotyping in 5,211 voluntary blood donors. *Hepatology* 2000;**31**:1160–4. (Location Canada.)

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. (No control group and no strategy comparison.)

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. (Location USA.)

Bartolo C, McAndrew PE, Sosolik RC, Cawley KA, Balcerzak SP, Brandt JT, *et al*. Differential diagnosis of hereditary hemochromatosis from other liver disorders by genetic analysis: gene mutation analysis of patients previously diagnosed with hemochromatosis by liver biopsy. *Arch Pathol Lab Med* 1998;**122**:633–7. (Location USA.)

Benn HP, Nielsen P, Fischer R, Schwarz D, Engelhardt R, Darda C, *et al*. Screening for hereditary hemochromatosis in prospective blood donors. *Beitr Infusionsther Transfusionsmed* 1994;**32**:314–6. (No control group and no strategy comparison.)

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**:329–37. (Location USA.)

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. (No control group and no strategy comparison.)

Cadet E, Capron D, Perez AS, Crepin SN, Arlot S, Ducroix JP, *et al*. A targeted approach significantly increases the identification rate of patients with undiagnosed haemochromatosis. *J Intern Med* 2003;**253**:217–24. (No strategy comparison.)

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. (Location Australia and no control group.)

Datz C, Lalloz MRA, Vogel W, Graziadei I, Hackl F, Vautier G, *et al*. Predominance of the HLA-H Cys282Tyr mutation in Austrian patients with genetic haemochromatosis. *J Hepatol* 1997;**27**:773–9. (Location Austria.)

Emery J, Rose P, Harcourt J, Livesey K, Merryweather-Clarke A, Pointon JJ, *et al*. Pilot study of early diagnosis of hereditary haemochromatosis through systematic case finding in primary care. *Community Genet* 2002;**5**:262–5. (No control group and unclear case definition.)

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. (No control group, no strategy comparison)

Guttridge MG, Carter K, Worwood M, Darke C. Population screening for hemochromatosis by PCR using sequence-specific primers. *Genet Test* 2000;**4**:111–14. (No control group and no strategy comparison.)

Hannuksela J, Niemela O, Leppilampi M, Parkkila AK, Koistinen P, Nieminen P, *et al*. Clinical utility and outcome of HFE-genotyping in the search for hereditary hemochromatosis. *Clin Chim Acta* 2003;**331**:61–7. (No control group and no strategy comparison.)

Jackson HA, Bowen DJ, Worwood M. Rapid genetic screening for haemochromatosis using heteroduplex technology. *Br J Haematol* 1997;**98**:856–9. (No control group and no strategy comparison.)

Jezequel P, Bargain M, Lellouche F, Geffroy F, Dorval I. Allele frequencies of hereditary hemochromatosis gene mutations in a local population of west Brittany. *Hum Genet* 1998;**102**:332–3. (No defined HHC group and no strategy comparison.)

Jorquera F, Dominguez A, az-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**:298–302. (Location Spain; excludes southern Europeans.)

Lombard M, Craven C, Spencer S, Crowe J. Predictive accuracy of biochemical tests for idiopathic hemochromatosis in an Irish population. *Ir J Med Sci* 1986;**155**:248–9. (No control group and no strategy comparison.)

Ludwig J, Batts KP, Moyer TP, Baldus WP, Fairbanks VF. Liver biopsy diagnosis of homozygous hemochromatosis: a diagnostic algorithm. *Mayo Clin Proc* 1993;**68**:263–7. (Liver biopsy study.)

McCune CA, Ravine D, Carter K, Jackson HA, Hutton D, Hedderich J, *et al*. Iron loading and morbidity among relatives of HFE C282Y homozygotes identified either by population genetic testing or presenting as patients. *Gut* 2006;**55**:554–62. (No control group and no strategy comparison.)

McGrath JS, Deugnier Y, Moirand R, Jouanolle AM, Chakrabarti S, Adams PC. A nomogram to predict C282Y hemochromatosis. *J Lab Clin Med* 2002;**140**:6–8. (Location Canada.)

Milman N, Koefoed P, Pedersen P, Nielsen FC, Eiberg H. Frequency of the HFE C282Y and H63D mutations in Danish patients with clinical haemochromatosis initially diagnosed by phenotypic methods. *Eur J Haematol* 2003;**71**:403–7. (No control group and no strategy comparison.)

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. (No control group and no strategy comparison.)

Mundy L, Merlin T, Bywood P, Parrella A. *MRI for the assessment of liver iron stores: management of patients with suspected or diagnosed haemochromatosis. Horizon Scanning Prioritising Summary – Volume 4*. Adelaide: Adelaide Health Technology Assessment (AHTA) on behalf of National Horizon Scanning Unit (HealthPACT and MSAC); 2004. (MRI for liver iron.)

Murtagh LJ, Whiley M, Wilson S, Tran H, Bassett ML. Unsaturated iron binding capacity and transferrin saturation are equally reliable in detection of HFE hemochromatosis. *Am J Gastroenterol* 2002;**97**:2093–9. (Location Australia and no control group and no strategy comparison.)

Njajou OT, Houwing-Duistermaat JJ, Osborne RH, Vaessen N, Vergeer J, Heeringa J, *et al*. A population-based study of the effect of the HFE C282Y and H63D mutations on iron metabolism. *Eur J Hum Genet* 2003;**11**:225–31. (No control group and no strategy comparison.)

O'Hara R, Cavanagh N, Cassidy M, Cullina M. The role of transferrin saturation as a screening test for hereditary haemochromatosis in an Irish population seeking medical care. *Ann Clin Biochem* 2003;**40**:169–74. (No control group and no strategy comparison.)

Palomaki GE, Haddow JE, Bradley LA, Richards CS, Stenzel TT, Grody WW. Estimated analytic validity of HFE C282Y mutation testing in population screening: the potential value of confirmatory testing. *Genet Med* 2003;**5**:440–3. (Location USA.)

Parks SB, Popovich BW, Press RD. Real-time polymerase chain reaction with fluorescent hybridization probes for the detection of prevalent mutations causing common thrombophilic and iron overload phenotypes. *Am J Clin Pathol* 2001;**115**:439–47. (Location USA.)

Patch C, Rosenberg W, Roderick P. Comparison of two screening strategies for haemochromatosis: a pilot study investigating uptake, feasibility and cost. *J Med Genet* 2001;**38**:S31. (No control group and population screening setting.)

Patch C, Roderick P, Rosenberg W. Prevalence and burden of disease in hemochromatosis: estimates derived from routine data. *Nurs Health Sci* 2006;**8**:128–9. (No control group and no strategy comparison.)

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. (No control group and no strategy comparison.)

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 [see comment]. *Am J Clin Pathol* 1998;**109**:577–84. (Location USA.)

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. (Location Australia and no control group and no strategy comparison.)

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. (No control group and no strategy comparison.)

Stave GM, Mignogna JJ, Powell GS, Hunt CM. Evaluation of a workplace hemochromatosis screening program. *Am J Prev Med* 1999;**16**:303–6. (Location USA.)

Watkins S, Thorburn D, Joshi NG, Neilson M, Joyce T, Spooner R, *et al*. Biochemical and clinical penetrance of individuals diagnosed with haemochromatosis by predictive genetic testing. *Gut* 2004;**53**:A86–7. (No control group and no strategy comparison.)

Whiting PW, Fletcher LM, Dixon JK, Gochee P, Powell LW, Crawford DH. Concordance of iron indices in homozygote and heterozygote sibling pairs in hemochromatosis families: implications for family screening. *J Hepatol* 2002;**37**:309–14. (Australia and no control group and no strategy comparison.)

Wrede CE, Hutzler S, Bollheimer LC, Buettner R, Hellerbrand C, Schoelmerich J, *et al*. Correlation between iron status and genetic hemochromatosis (codon C282Y) in a large German population. *Isr Med Assoc J* 2004;**6**:30–3. (No control group and no strategy comparison.)

Psychosocial aspects

Anderson RT, Press N, Tucker DC, Snively BM, Wenzel L, Ellis SD, *et al*. Patient acceptability of genotypic testing for hemochromatosis in primary care. *Genet Med* 2005;**7**:557–63. (Subjects had not been diagnosed with haemochromatosis; population screening context.)

Bassett M, Dunn C, Battese K, Peek M. Acceptance of neonatal genetic screening for hereditary hemochromatosis by informed parents. *Genet Test* 2001;**5**:317–20. (Subjects had not been diagnosed with haemochromatosis; prenatal screening context.)

Gason AA, Aitken MA, Metcalfe SA, Allen KJ, Delatycki MB. Genetic susceptibility screening in schools: attitudes of the school community towards hereditary haemochromatosis. *Clin Genet* 2005;**67**:166–74. (Subjects had not been diagnosed with haemochromatosis; school pupils attitudes to screening.)

Hall MA, McEwen JE, Barton JC, Walker AP, Howe EG, Reiss JA, *et al*. Concerns in a primary care population about genetic discrimination by insurers. *Genet Med* 2005;**7**:311–6. (Subjects had not been diagnosed with haemochromatosis; population screening context.)

Hicken BL, Calhoun DC, Tucker DC. Genetic testing for hemochromatosis: attitudes and acceptability among young and older adults. *Genet Test* 2003;**7**:235–9. (Subjects had not been diagnosed with haemochromatosis.)

Hicken BL, Foshee A, Tucker DC. Perceptions and attitudes about HFE genotyping among college-age adults. *J Genet Couns* 2005;**14**:465–72. (Subjects had not been diagnosed with haemochromatosis.)

Paglierani LM, Kalkwarf HJ, Rosenthal SL, Huether CA, Wenstrup RJ. The impact of test outcome certainty on interest in genetic testing among college women. *J Genet Couns* 2003;**12**:131–50. (Subjects had not been diagnosed with haemochromatosis.)

Patch C, Roderick P, Rosenberg W. Comparison of genotypic and phenotypic strategies for population screening in hemochromatosis: assessment of anxiety, depression, and perception of health. *Genet Med* 2005;**7**:550–6. (Subjects had not been diagnosed with haemochromatosis; population screening context.)

Patch C, Roderick P, Rosenberg W. Factors affecting the uptake of screening: a randomised controlled non-inferiority trial comparing a genotypic and a phenotypic strategy for screening for haemochromatosis [see comment]. *J Hepato*l 2005;**43**:149–55. (Subjects had not been diagnosed with haemochromatosis; population screening context.)

Patch C, Roderick P, Rosenberg W. Feasibility and acceptability of two screening strategies for haemochromatosis, report of phase one of a randomised controlled trial. *Eur J Hum Genet* 2002;**10**:309. (Subjects had not been diagnosed with haemochromatosis; population screening context.)

Patch C, Roderick P, Rosenberg WM. Psychological effects of genetic and biochemical population screening for hemochromatosis. *Hepatology* 2004;**40**:576A. (Subjects had not been diagnosed with haemochromatosis; population screening context.)

Power TE, Adams PC. Psychosocial impact of genetic testing for hemochromatosis in population screening and referred patients. *Hepatology* 2000;**32**:413A. (Abstract; full paper available and is included.)

Salkovskis PM, Dennis R, Wroe AL. An experimental study of influences on the perceived likelihood of seeking genetic testing: 'nondirectiveness' may be misleading. *J Psychosom Res* 1999;**47**:439–47. (Subjects had not been diagnosed with haemochromatosis; population screening context.)

Shaheen NJ, Lawrence LB, Bacon BR, Barton JC, Barton NH, Galanko J, *et al*. Insurance, employment, and psychosocial consequences of a diagnosis of hereditary hemochromatosis in subjects without end organ damage. *Am J Gastroenterol* 2003;**98**:1175–80. (Not about impact of genetic testing; impact of HC diagnosis.)

Stuhrmann M, Hoy L, Nippert I, Schmidtke J. Genotype-based screening for hereditary hemochromatosis: II. Attitudes toward genetic testing and psychosocial impact – a report from a German pilot study. *Genet Test* 2005;**9**:242–54. (Population screening context.)

Tucker DC, Acton RT, Press N, Ruggiero A, Reiss JA, Walker AP, *et al*. Predictors of belief that genetic test information about hemochromatosis should be shared with family members. *Genet Test* 2006;**10**:50–9. (Subjects had not been diagnosed with haemochromatosis; population screening context.)

Epidemiology

Andrikovics H, Kalmar L, Bors A, Fandl B, Petri I, Kalasz L, *et al*. Genotype screening for hereditary hemochromatosis among voluntary blood donors in Hungary. *Blood Cells Mol Dis* 2001;**27**:334–41. (Location Hungary.)

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. (Location USA.)

Barton JC, Acton RT, Dawkins FW, Adams PC, Lovato L, Leiendecker-Foster C, *et al*. Initial screening transferrin saturation values, serum ferritin concentrations, and HFE genotypes in whites and blacks in the Hemochromatosis and Iron Overload Screening Study. *Genet Test* 2005;**9**:231–41. (Location USA.)

Barton JC, Acton RT, Lovato L, Speechley MR, McLaren CE, Harris EL, *et al*. Initial screening transferrin saturation values, serum ferritin concentrations, and HFE genotypes in Native Americans and whites in the Hemochromatosis and Iron Overload Screening Study. *Clin Genet* 2006;**69**:48–57. (Location USA.)

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. (Location Norway.)

Bradley LA, Johnson DD, Palomaki GE, Haddow JE, Robertson NH, Ferrie RM. Hereditary haemochromatosis mutation frequencies in the general population. *J Med Screen* 1998;**5**:34–6. (Location USA.)

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**:830–6. (Location New Zealand.)

Distante S, Berg JP, Lande K, Haug E, Bell H. High prevalence of the hemochromatosis-associated Cys282Tyr *HFE* gene mutation in a healthy Norwegian population in the city of Oslo, and its phenotypic expression. *Scand J Gastroenterol* 1999;**34**:529–34. (Location Norway.)

Hallberg L, Bjorn-Rasmussen E, Jungner I. Prevalence of hereditary haemochromatosis in two Swedish urban areas. *J Intern Med* 1989;**225**:249–55. (Location Sweden.)

Holmstrom P, Marmur J, Eggertsen G, Gafvels M, Stal P. Mild iron overload in patients carrying the HFE S65C gene mutation: a retrospective study in patients with suspected iron overload and healthy controls. *Gut* 2002;**51**:723–30. (Location Sweden.)

Milman N, Pedersen P, Steig T, Melsen GV. Frequencies of the hereditary hemochromatosis allele in different populations. Comparison of previous phenotypic methods and novel genotypic methods. *Int J Hematol* 2003;**77**:48–54. (Review.)

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. (Location France.)

Nielsen P, Carpinteiro S, Fischer R, Cabeda JM, Porto G, Gabbe EE. Prevalence of the C282Y and H63D mutations in the *HFE* gene in patients with hereditary haemochromatosis and in control subjects from Northern Germany. *Br J Haematol* 1998;**103**:842–5. (Location Germany.)

Patch C, Roderick P, Rosenberg W. Prevalence and burden of disease in hemochromatosis: estimates derived from routine data. *Nurs Health Sci* 2006;**8**;**128**–9. (Estimates derived from routine data.)

Willis G, Wimperis JZ, Smith K, Fellows IW, Jennings BA. HFE mutations in the elderly. *Blood Cells Mol Dis* 2003;**31**:240–6. (Restricted to elderly population.)

Merryweather-Clarke AT, Pointon JJ, Shearman JD, Robson KJ. Global prevalence of putative haemochromatosis mutations. *J Med Genet* 1997;**34**:275–8. (Review.)

Liver biopsy

Bicknell SG, Richenberg J, Cooperberg PL, Tiwari P, Halperin L. Early discharge after core liver biopsy: is it safe and cost-effective? *Can Assoc Radiol J* 2002;**53**:205–9. (Not an RCT.)

Chuah SY. Liver biopsy – past, present and future. *Singapore Med J* 1996;**37**:86–90. (Not an RCT.)

Farrell RJ, Smiddy PF, Pilkington RM, Tobin AA, Mooney EE, Temperley IJ, *et al*. Guided versus blind liver biopsy for chronic hepatitis C: clinical benefits and costs. *J Hepatol* 1999;**30**:580–7. (Participants had hepatitis C.)

Froehlich F, Lamy O, Fried M, Gonvers JJ. Practice and complications of liver biopsy. Results of a nationwide survey in Switzerland. *Dig Dis Sci* 1993;**38**:1480–4. (Not an RCT.)

Gilmore IT, Burroughs A, Murray-Lyon IM, Williams R, Jenkins D, Hopkins A. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. *Gut* 1995;**36**:437–41. (Not an RCT.)

Janes CH, Lindor KD. Outcome of patients hospitalized for complications after outpatient liver biopsy. *Ann Intern Med* 1993;**118**:96–8. (Not an RCT.)

Kavanagh G, McNulty J, Fielding JF. Complications of liver biopsy: the incidence of pneumothorax and role of post biopsy chest x-ray. *Ir J Med Sci* 1991;**160**:387–8. (Not an RCT.)

Pasha T, Gabriel S, Therneau T, Dickson ER, Lindor KD. Cost-effectiveness of ultrasound-guided liver biopsy. *Hepatology* 1998;**27**:1220–6. (Not an RCT.)

Piccinino F, Sagnelli E, Pasquale G, Giusti G. Complications following percutaneous liver biopsy. A

multicentre retrospective study on 68,276 biopsies. *J Hepatol* 1986;**2**:165–73. (Not an RCT.)

Pokorny CS, Waterland M. Short-stay, out-of-hospital, radiologically guided liver biopsy [see comment]. *Med J Aust* 2002;**176**:67–9. (Not an RCT.)

Pongchairerks P. Ultrasound-guided liver biopsy: accuracy, safety and sonographic findings. *J Med Assoc Thailand* 1993;**76**:597–600. (Not an RCT.)

Smith BC, Desmond PV. Outpatient liver biopsy using ultrasound guidance and the Biopty gun is safe and cost-effective. *Aust N Z J Med* 1995;**25**:209–11. (Not an RCT.)

Stone MA, Mayberry JF. An audit of ultrasound guided liver biopsies: a need for evidence-based practice. *Hepatogastroenterology* 1996;**43**:432–4. (Not an RCT.)

Stotland BR, Lichtenstein GR. Liver biopsy complications and routine ultrasound. *Am J Gastroenterol* 1996;**91**:1295–6. (Editorial.)

Terjung B, Lemnitzer I, Dumoulin FL, Effenberger W, Brackmann HH, Sauerbruch T, *et al*. Bleeding complications after percutaneous liver biopsy. An analysis of risk factors. *Digestion* 2003;**67**:138–45. (Not an RCT.)

Tobkes AI, Nord HJ. Liver biopsy: review of methodology and complications. *Dig Dis* 1995;**13**:267–74. (Not an RCT.)

Van Thiel DH, Gavaler JS, Wright H, Tzakis A. Liver biopsy. Its safety and complications as seen at a liver transplant center. *Transplantation* 1993;**55**:1087–90. (Not an RCT.)

Vivas S, Palacio MA, Rodriguez M, Lomo J, Cadenas F, Giganto F, *et al*. Ambulatory liver biopsy: complications and evolution in 264 cases. *Rev Esp Enferm Dig* 1998;**90**:175–82. (Not an RCT.)

Wawrzynowicz-Syczewska M, Kruszewski T, Boron-Kaczmarska A. Complications of percutaneous liver biopsy. *Rom J Gastroenterol* 2002;**11**:105–7. (Not guided liver biopsies.)

Younossi ZM, Teran JC, Ganiats TG, Carey WD. Ultrasound-guided liver biopsy for parenchymal liver disease: an economic analysis. *Dig Dis Sci* 1998;**43**:46–50. (Not an RCT.)

Cost-effectiveness studies

Adams PC, Kertesz AE, Valberg LS. Screening for hemochromatosis in children of homozygotes: prevalence and cost-effectiveness. *Hepatology* 1995;**22**:1720–7. (Not DNA testing.)

Killeen AA, Miller PJ. Universal screening for hereditary hemochromatosis in the United States: a cost–benefit analysis. *Clin Chem* 2002;**48**:A175. (Screening study.)

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. (Not economic evaluation.)

Pardo A. Cost-effectiveness of genetic diagnosis for hereditary hemochromatosis screening. *Gastroenterology* 2000;**118**:A1405. (Screening study.)

Phatak PD, Guzman G, Woll JE, Robeson A, Phelps CE. Cost-effectiveness of screening for hereditary hemochromatosis. *Arch Intern Med* 1994;**154**:769–76. (Screening – transferrin saturation; serum ferritin.)

Talwalkar J, Torgerson H, Malinchoc M, Brandhagen D. Health-related quality of life assessment in hereditary hemochromatosis. *Hepatology* 2003;**38**:663A. (Not economic evaluation.)

Appendix 4

Ongoing studies identified from the National Research Register

UK Women's Cohort Study phase 2

NRR data provider: Leeds Teaching Hospitals NHS Trust.

Region: Northern/Yorkshire Regional Office.

Project number: N0436165676.

Principal research question: To determine the relationship between iron intake, iron status and the risk of iron overload in subjects who are heterozygous (and homozygous) for two genetic mutations (C282Y and H63D) associated with haemochromatosis compared with subjects without these mutations.

Lead centre name: University of Leeds.

Start date: 1 May 2000.

End date: 30 December 2007 [ongoing at time of writing].

Project status: Ongoing.

Funding organisation name: Food Standards Agency.

Funding amount: £250,000.

Funding organisation name: NHS R&D Support Funding.

Funding reference number: 2007/08.

Appendix 5

Quality assessment of experimental studies

Quality assessment of clinical validity studies[a]

Item	Judgement[b]
1. Were selection criteria for eligibility of patients objective and clearly described to allow replication?	
2. Is the definition of iron overload likely to correctly classify HHC?	
3. Did the study use proper sampling so that all patients were equally likely to enter the study?	
4. Was the control population appropriate and clearly described?	
5. Did the study use proper sampling so that all control subjects were equally likely to enter the study?	
6. Was the DNA test method described in sufficient detail to permit replication?	
7. Was the execution of biochemical methods described in sufficient detail to permit replication?	
8. Were groups under comparison comparable in terms of age, sex and race?	
9. Was there any mention of missing data?	
10. Was the sample of patients representative of the patients who will receive the test in practice, i.e. are results generalisable?	

a Modified from QUADAS[80] and Spitzer *et al*.[81]
b Given as yes, no or unclear.

Appendix 6

Quality assessment of observational studies

An assessment was used for included studies that were not RCTs. These quality criteria were adapted from Spitzer and colleagues.[81] The original checklist was modified to include items of particular relevance to assessing observational studies.

1. Does the trial use proper random assignment? A study with proper random assignment would include multiple conditions with random assignment and would use an appropriate method for the assignment (e.g. random numbers table, computer generated, etc.) with allocation concealment.
2. Did the study use proper sampling? A study with proper sampling would allow for all patients to be equally likely to enter the study (e.g. patients selected consecutively or randomly sampled).
3. Was the sample size adequate? A proper sample size enables adequately precise estimates of priority variables found to be significant (e.g. can compute confidence intervals within relatively small range or relatively small SEM).
4. Were the criteria for definition or measurement of outcomes objective or verifiable? Good outcome measures would be defined by clear methods for measuring outcomes (i.e. an operational definition) that are public, verifiable and repeatable.
5. Were outcomes measured with blind assessment? In studies with blind assessment those evaluating outcomes are unaware of the treatment status of those being evaluated.
6. Were objective criteria used for the eligibility of subjects? Good eligibility criteria would use clear, public, verifiable characteristics, which are applied for inclusion and exclusion.
7. Were attrition rates (%) provided? A study should report the number of patients who could not be contacted for outcome measures or later, e.g. dropouts or withdrawals because of treatment toxicity.
8. Were groups under comparison comparable? Comparable groups show similar results across a reasonable range of baseline characteristics that could be expected to affect results.
9. Are the results generalisable? Generalisable results come from a sample population that is representative of the population to which results would be applied.

Appendix 7

Data extraction of clinical validity studies

Reference and design	Intervention	Participants	Outcome measures
Author: Cardoso *et al*.[87] Year: 1998 Country: Sweden Study design: Cohort with control Number of centres: One Funding: Swedish Medical Research Council, Swedish Society of Medicine, Ruth and Richard Julins Foundation and the Karolinska Institute	Tests: DNA tests (C282Y and H63D)	Number of participants: Intervention: 87 with HHC; control: 117 random healthy Swedish subjects Sample attrition/dropout: None Inclusion criteria for study entry: High transferrin saturation (> 60% in men and > 50% in women) and increased ferritin levels > 300 µg/l and a liver biopsy with typical iron staining indicating primary HHC Exclusion criteria for study entry: Siblings of patients with HHC in the study were excluded Characteristics of participants: 67 men with mean age of 47 (range 20–73) years and 20 women with mean age of 49 years (range 25–72)	Primary outcome: Frequency of C282Y and H63D mutations Secondary outcomes: Method of assessing outcomes: Molecular genetic analyses of the *HFE* gene (PCR followed by enzyme restriction) were performed in genomic DNA from unrelated patients and in healthy subjects Adverse symptoms: n/a Length of follow-up: n/a Recruitment dates: Not stated

Results

Primary outcome	Intervention HHC	Control	*p*-value
C282Y	164	9	< 0.001
H63D	6	29	< 0.01
Other	4	196	
Comments			

C282Y homozygosity	Iron overload population (defined)		Control population		Total	
Yes, DNA test positive	a	80	b	0	a+b	80
No, DNA test negative	c	7	d	117	c+d	124
Total	a+c	87	b+d	117	a+b+c+d	204

Calculate clinical sensitivity, specificity, PPV and NPV if possible and note whether this agrees with any of these values that are reported in the text of the paper:

Clinical sensitivity = a/a + c = 80/87 × 100 = 92%

Clinical specificity = d/b + d = 117/117 × 100 = 100%

PPV = a/a + b = 80/80 × 100 = 100%

NPV = d/c + d = 117/124 × 100 = 94.4%

Comments: Of the patients, 92% were homozygous and 4.5% were heterozygous for the C282Y mutation

Quality assessment by modified QUADAS[80] and Spitzer *et al*.[81]		
Item		**Judgement**[a]
1.	Were selection criteria for eligibility of patients objective and clearly described?	Y
2.	Is the definition of iron overload likely to correctly classify HHC?	Y
3.	Did the study use proper sampling so that all patients were equally likely to enter the study?	U
4.	Was the control population appropriate?	U
5.	Did the study use proper sampling so that all control subjects were equally likely to enter the study?	Y
6.	Was the DNA test described in sufficient detail to permit replication?	Y
7.	Was the execution of the biochemical methods described in sufficient detail to permit replication?	N (no details)
8.	Were the groups under comparison comparable in terms of age, sex and race?	U
9.	Was there any mention of missing data?	N
10.	Was the sample of patients representative of the patients who will receive the test in practice, i.e. are the results generalisable?	Y

a Y, yes; N, no; U, unclear.

Reference and design	Intervention	Participants	Outcome measures
Author: Hellerbrand *et al*.[88] Year: 2001 Country: Germany Study design: Cohort with control Number of centres: One Funding: None stated	Tests: DNA tests (C282Y and H63D)	Number of participants: Intervention: 36 unrelated HHC patients; control: 126 healthy hospital employees Sample attrition/dropout: None Sample crossovers: n/a Inclusion criteria for study entry: The diagnosis of haemochromatosis was based on clinical history and exclusion of other causes of iron overload. Criteria for HHC: (1) increased transferrin saturation (repeatedly > 50%) and elevated serum ferritin levels, (2) hepatocellular haemosiderin deposits of grade III–IV, (3) hepatic iron index (HII) > 1.9 and/or total amount of iron removed (IR) > 5 g in men (> 3 g in women) Exclusion criteria for study entry: Chronic viral hepatitis infection Characteristics of participants: 10 women and 26 men with a mean age of 56 ± 13 years. All patients were Caucasian and their geographical origin was southern Germany	Primary outcomes: Frequency of C282Y and H63D mutations Secondary outcomes: None Method of assessing outcomes: Mutations detected using single-stranded conformation polymorphism analysis for capillary electrophoresis and restriction length polymorphism Adverse symptoms: None Length of follow-up: n/a Recruitment dates: n/a

Results

Primary outcomes

C282Y	H63D	Intervention, *n*	Control, *n*	*p*-value
+/+	–/–	26	0	
+/–	+/–	3	0	
+/–	–/–	2	6	
–/–	–/–	2	88	
–/–	+/–	2	29	
–/–	+/–	1	3	

Comments:

C28Y homozygosity	Iron overload population (defined)		Control population		Total	
Yes, DNA test positive	a	26	b	0	a+b	26
No, DNA test negative	c	10	d	126	c+d	136
Total	a+c	36	b+d	126	a+b+c+d	162

Calculate clinical sensitivity, specificity, PPV and NPV if possible and note whether this agrees with any of these values that are reported in the text of the paper:

Clinical sensitivity = a/a + c = 26/36×100 = 72.2%

Clinical specificity = d/b + d = 126/126×100 = 100%

PPV = a/a + b = 26/26×100 = 100%

NPV = d/c + d = 126/136×100 = 92.7%

Comments: 72.2% were homozygous for the C282Y mutation.

Quality assessment by modified QUADAS[80] and Spitzer *et al.*[81]

Item		Judgement[a]
1.	Were selection criteria for eligibility of patients objective and clearly described?	Y
2.	Is the definition of iron overload likely to correctly classify HHC?	Y
3.	Did the study use proper sampling so that all patients were equally likely to enter the study?	U
4.	Was the control population appropriate?	N
5.	Did the study use proper sampling so that all control subjects were equally likely to enter the study?	U
6.	Was the DNA test described in sufficient detail to permit replication?	Y
7.	Was the execution of the biochemical methods described in sufficient detail to permit replication?	N
8.	Were the groups under comparison comparable in terms of age, sex and race?	U
9.	Was there any mention of missing data?	N
10.	Was the sample of patients representative of the patients who will receive the test in practice, i.e. are the results generalisable?	Y

a Y, yes; N, no; U, unclear.

Reference and design	Intervention	Participants	Outcome measures
Author: Holmstrom *et al*.[89] Year: 2002 Country: Sweden Study design: Controlled cohort study Number of centres: One Funding: Swedish Medical Research Council, Swedish Society of Medicine, Nanna Svartz Foundation, Ragnhild and Einar Lundstroms Memory Foundation	Tests: DNA tests (C282Y, H63D and S65C); serum levels of ferritin, transferrin and iron; total haemoglobin; iron staining of liver biopsies (if performed) and phlebotomy treatment details extracted from files for 231 of 296 patients	Number of participants: Iron overload cohort: 296 Control cohort: 250 Sample attrition/dropout: Iron overload cohort: In 78 cases the exact serum ferritin value at the time of diagnosis could not be found and in 90 patients data on transferrin saturation were missing Control cohort: Not reported Sample crossovers: Not applicable Inclusion criteria for study entry: Iron overload cohort: Participants were selected from those genotyped for *HFE* mutations at the study hospital from 1 October 1997 to 19 September 2000. All had either (1) serum ferritin > 300 μg/l (men) or > 200 μg/l (women) or (2) transferrin saturation > 50% (men) or > 45% (women). Patients with hepatic iron staining of grade 1 or more or who had been treated with phlebotomies were classified as having iron overload Control cohort: Not specified but were recruited from hospital staff, students, and their relatives and none had a history of liver disease or had received multiple blood transfusions Exclusion criteria for study entry: Iron overload cohort: Those patients found by family screening or those related to another subject in the study. A further 17 patients were excluded who had hyperferritinaemia because of acute hepatitis, acute liver failure, hepatocellular carcinoma, thyrotoxicosis, acute leukaemia or myelodysplastic syndrome Control cohort: None specified Characteristics of participants: Iron overload cohort: Mean age: 54.5 (SD 14.8) years; female: 39% Control cohort: Mean age: 47.7 (SD 17.9) years; female: 64%	Primary outcome: Frequencies of C282Y, H63D and S65C *HFE* genotypes in patient and control cohorts Secondary outcomes: Iron overload in relation to genotype; biochemical iron parameters and clinical data in relation to S65C mutation; *HFE* mutations and biochemical iron parameters in members of one family Method of assessing outcomes: (1) Mutation analysis: human genomic DNA was extracted from peripheral blood leucocytes Iron overload cohort: Identification of mutations in the *HFE* gene by automatic DNA sequence determination, corresponding to the first half of exon 2 and the whole of exon 4. The ABI Prism Big Dye Primer Cycle Sequencing Kit on an ABI Prism 377 DNA Sequencer (PE Applied Biosystems) was used Control cohort: Identification of mutations in the *HFE* gene carried out by restriction fragment length polymorphism (RFLP). Following electrophoresis on precast polyacrylamide gels bands were visualised by silver staining using the PlusOne DNA Silver Staining kit (Pharmacia Biotech AB). All substitutions detected by RFLP were confirmed, either by repeating RFLP testing (C282Y) or by automatic sequence analysis (H63D, S65C) (2) Biochemical analysis: serum levels of ferritin, transferrin and iron determined by automated turbidimetry/nephelometry or spectrophototometry. Transferrin saturation calculated according to the formula 4(p – iron/p – transferrin). Total haemoglobin value determined on whole blood samples Iron overload cohort: Values for serum ferritin and/or transferrin saturation and haemoglobin count collected retrospectively from patient files from the time of diagnosis (before initiation of phlebotomy treatment) Control cohort: Serum ferritin, transferrin saturation and haemoglobin count analysed from blood samples collected from each participant Adverse symptoms: None reported Length of follow-up: No follow-up Recruitment dates: Not reported

Results

Primary outcomes	Iron overload cohort ($n = 296$), n (%)	Control cohort ($n = 250$), n (%)	p-value
C282Y, C282Y	84 (28.4)	1 (0.4)	<0.001
C282Y, wt*	30 (10.1)	27 (10.8)	<0.001
C282Y, H63D	21 (7.1)	2 (0.8)	
H63D, H63D	7 (2.4)	7 (2.8)	
H63D, wt*	52 (17.6)	41 (16.4)	
wt, wt*	102 (34.5)	172 (68.8)	

Comments: Original results table included separate results for the S65C mutation in combination with C282Y, H63D or wt. Results above marked with * calculated by reviewer by combining the S65C results with those for C282Y and H63D and wt

The paper also reports that the TfR2 Y205X mutation could not be detected in any of the 44 patients in whom this was investigated

C28Y homozygosity	Iron overload population (defined) ($n = 296$)		Control population ($n = 250$)		Total	
Yes, DNA test positive	a	84	b	1	a+b	85
No, DNA test negative	c	212	d	249	c+d	461
Total	a+c	296	b+d	250	a+b+c+d	546

Calculate clinical sensitivity, specificity, PPV and NPV if possible and note whether this agrees with any of these values that are reported in the text of the paper:

Clinical sensitivity = a/a + c = 84/296 × 100 = 28.4%

Clinical specificity = d/b + d = 249/250 × 100 = 99.6%

PPV = a/a + b = 84/85 × 100 = 98.8%

NPV = d/c + d = 249/461 × 100 = 54.0%

Comments:

Quality assessment by modified QUADAS[80] and Spitzer *et al.*[81]

Item		Judgement[a]
1.	Were selection criteria for eligibility of patients objective and clearly described?	Y
2.	Is the definition of iron overload likely to correctly classify HHC?	U
3.	Did the study use proper sampling so that all patients were equally likely to enter the study?	U
4.	Was the control population appropriate?	N
5.	Did the study use proper sampling so that all control subjects were equally likely to enter the study?	U
6.	Was the DNA test described in sufficient detail to permit replication?	Y
7.	Was the execution of the biochemical methods described in sufficient detail to permit replication?	U
8.	Were the groups under comparison comparable in terms of age, sex and race?	N
9.	Was there any mention of missing data?	Y
10.	Was the sample of patients representative of the patients who will receive the test in practice, i.e. are the results generalisable?	U

a Y, yes; N, no; U, unclear.

Reference and design	Intervention	Participants	Outcome measures
Author: Jouanolle *et al*.[90] Year: 1997 Country: France Study design: Controlled cohort study Number of centres: Not stated Funding: In part by the Association Francaise Contre les Myopathies and the Fondation Langlois	Tests: DNA tests (C282Y and H63D) Other interventions used: Haplotype analysis	Number of participants: Genetic haemochromatosis cohort: 132; random control cohort: 139; first-degree relatives: 30 Sample attrition/dropout: Not reported Sample crossovers: Not applicable Inclusion criteria for study entry: Genetic haemochromatosis cohort: Participants had been diagnosed with genetic haemochromatosis during the period 1968–89. Diagnosis was based on clinical and biological signs in the absence of any cause of secondary iron overload with at least one of (1) increased stainable iron in at least 75% of hepatocytes, (2) hepatic iron concentration > 100 μmol/g dry weight, (3) hepatic iron index > 2 and (4) > 5 g of iron removed by weekly phlebotomy. Most of the patients were clinically affected and/or had a family history of haemochromatosis Random control cohort: Not specified but came from the general population First-degree relatives: Spouses or siblings of the haemochromatosis patients described above. These participants had (1) no sign of iron overload and (2) each of his/her haplotype recognised in at least one other relative sharing one haplotype with the proband without any evidence of iron overload Exclusion criteria for study entry: None specified for any group of participants Characteristics of participants: Not described for any group of participants	Primary outcome: Frequencies of C282Y and H63D *HFE* genotypes in patient and control cohorts, and in first-degree relatives Secondary outcomes: Haplotype analysis Method of assessing outcomes: Mutation analysis: DNA was prepared from whole blood; C282Y and H63D loci were analysed in control and patient groups by fluorescent sequencing and the C282Y and H63D mutations were then screened using enzymatic digestion of PCR products (RFLP analysis); five microsatellite markers, D6S510, HLA-F, MOG, D6S105 and D6S1260, were analysed by PCR Adverse symptoms: None reported Length of follow-up: No follow-up Recruitment dates: Not reported

Results

Primary outcomes	Iron overload cohort ($n = 132$), *n* (%)	Control cohort ($n = 139$), *n* (%)	First-degree relatives cohort ($n = 30$), *n* (%)
C282Y, C282Y	122 (92.4)	0 (0)	0 (0)
C282Y, wt*	3 (2.3)	5 (3.6)	0 (0)
C282Y, H63D	3 (2.3)	3 (2.2)	0 (0)
H63D, H63D	2 (1.5)	5 (3.6)	0 (0)
H63D, wt*	2 (1.5)	33 (23.7)	9 (30)
wt, wt*	0 (0)	93 (66.9)	21 (70)

Comments: The paper does not report on statistical differences between groups and no *p*-values are presented

C28Y homozygosity	Iron overload population (defined) (n = 132)		Control population (n = 139)		Total	
Yes, DNA test positive	a	122	b	0	a+b	122
No, DNA test negative	c	10	d	139	c+d	149
Total	a+c	132	b+d	139	a+b+c+d	271

Calculate clinical sensitivity, specificity, PPV and NPV if possible and note whether this agrees with any of these values that are reported in the text of the paper:

Clinical sensitivity = a/a + c = 122/132 × 100 = 92.4%

Clinical specificity = d/b + d = 139/139 × 100 = 100%

PPV = a/a + b = 122/122 × 100 = 100%

NPV = d/c + d = 139/149 × 100 = 93.3%

Comments:

Quality assessment by modified QUADAS[80] and Spitzer *et al.*[81]

Item		Judgement[a]
1.	Were selection criteria for eligibility of patients objective and clearly described?	Y
2.	Is the definition of iron overload likely to correctly classify HHC?	Y
3.	Did the study use proper sampling so that all patients were equally likely to enter the study?	U
4.	Was the control population appropriate?	N (no information)
5.	Did the study use proper sampling so that all control subjects were equally likely to enter the study?	Y
6.	Was the DNA test described in sufficient detail to permit replication?	Y
7.	Was the execution of the biochemical methods described in sufficient detail to permit replication?	n/a
8.	Were the groups under comparison comparable in terms of age, sex and race?	U
9.	Was there any mention of missing data?	N
10.	Was the sample of patients representative of the patients who will receive the test in practice, i.e. are the results generalisable?	Y

a Y, yes; N, no; U, unclear; n/a, not applicable.

Reference and design	Intervention	Participants	Outcome measures
Author: Mura *et al*.[91] Year: 2005 Country: France Study design: Controlled cohort study Number of centres: Not stated Funding: Institut National de la Santé et de la Recherche Médicale	Tests: DNA tests (C282Y, H63D and S65C); iron status based on transferrin saturation, ferritin concentration and serum iron concentration Other interventions used: None reported	Number of participants: Haemochromatosis cohort: 478; control cohort: 410; other patients: 3047 Sample attrition/dropout: Not reported Sample crossovers: Not applicable Inclusion criteria for study entry: Haemochromatosis cohort: This cohort included people diagnosed before and after the *HFE* gene was cloned in 1996. Before the *HFE* gene was cloned clinical diagnosis of haemochromatosis was based on classic signs and symptoms of the disease: (1) elevated transferrin saturation and/or serum ferritin concentration, (2) hepatic symptoms, such as unexplained elevation of serum liver enzymes, cirrhosis, liver failure, or diabetes mellitus and (3) non-specific compatible symptoms: fatigue, abdominal pain, joint pain, cardiac arrhythmia and hyperpigmentation. DNA testing was performed retrospectively in this group. Since the discovery of the *HFE* gene, patients have undergone DNA testing prospectively because of iron parameters elevated above the normal values [transferrin saturation > 45%, serum ferritin > 400 µg/l (men) or > 300 µg/l (women)], whether associated or not with other symptom(s) that could suggest HHC, or on cascade family testing Control cohort: Randomly selected but no further information is provided Other patients: This group included people who had an incidental finding of an elevated serum iron parameter and/or a family history of haemochromatosis Exclusion criteria for study entry: Characteristics of participants: All participants were from Brittany and of Caucasian origin. No other characteristics are reported	Primary outcome: Frequencies of C282Y, H63D and S65C *HFE* genotypes in patient and control cohorts Secondary outcomes: Comparison of age and serum iron parameters displayed at diagnosis by patients clinically diagnosed before *HFE* gene test availability with those subjected to a prospective *HFE* gene test DNA analysis: DNA extracted from peripheral blood leukocytes; *HFE* mutations C282Y, H63D and S65C analysed by an RFLP method described in earlier papers. Part of exon 2 or 4 was amplified by PCR and the PCR products were then enzymatically digested Iron status: Haemochromatosis cohort: Transferrin saturation, ferritin concentration and serum iron concentration was determined before the start of therapeutic phlebotomies Adverse symptoms: None reported Length of follow-up: No follow-up Recruitment dates: Other patients were included over a 5-year period (from 1997 to mid-2002) and tested prospectively

Results

Primary outcomes	Haemochromatosis cohort (*n* = 478), *n* (%)	Control cohort (*n* = 410), *n* (%)	Other patients (*n* = 3047)
C282Y, C282Y	388 (81.17)	2 (0.49)	561 (18.41)
C282Y, wt*	22 (4.60)	50 (12.20)	656 (21.53)
C282Y, H63D	32 (6.69)	9 (2.20)	311 (10.21)
H63D, H63D	6 (1.26)	3 (0.73)	106 (3.48)
H63D, wt*	11 (2.30)	100 (24.39)	486 (15.95)
wt, wt*	19 (3.97)	246 (60.00)	927 (30.42)

Comments: Original results table included separate results for the S65C mutation in combination with C282Y, H63D or wt. Results above marked with * calculated by reviewer by combining the S65C results with those for C282Y and H63D and wt. Results for other patients were divided into five time bands; these have been merged by the reviewer to give the results for the group over the whole time period. All percentage values also calculated by reviewer

Original results also present calculated expected genotype frequencies with confidence intervals, calculated from the observed allele frequencies

The paper does not report on statistical differences between groups and no *p*-values are presented

C28Y homozygosity	**Iron overload population (defined)**		**Control population**		**Total**	
Yes, DNA test positive	a	388	b	2	a+b	390
No, DNA test negative	c	90	d	408	c+d	498
Total	a+c	478	b+d	410	a+b+c+d	888

Calculate clinical sensitivity, specificity, PPV and NPV if possible and note whether this agrees with any of these values that are reported in the text of the paper:

Clinical sensitivity = a/a + c = 388/478 × 100 = 81.2%

Clinical specificity = d/b + d = 408/410 × 100 = 99.5%

PPV = a/a + b = 388/390 × 100 = 99.5%

NPV = d/c + d = 408/498 × 100 = 81.9%

Comments:

Quality assessment by modified QUADAS[80] and Spitzer *et al.*[81]

Item		**Judgement[a]**
1.	Were selection criteria for eligibility of patients objective and clearly described?	U
2.	Is the definition of iron overload likely to correctly classify HHC?	U
3.	Did the study use proper sampling so that all patients were equally likely to enter the study?	U
4.	Was the control population appropriate?	Y
5.	Did the study use proper sampling so that all control subjects were equally likely to enter the study?	Y
6.	Was the DNA test described in sufficient detail to permit replication?	Y
7.	Was the execution of the biochemical methods described in sufficient detail to permit replication?	N
8.	Were the groups under comparison comparable in terms of age, sex and race?	U
9.	Was there any mention of missing data?	N
10.	Was the sample of patients representative of the patients who will receive the test in practice, i.e. are the results generalisable?	U

a Y, yes; N, no; U, unclear.

Reference and design	Intervention	Participants	Outcome measures
Author: Murphy *et al*.[62] Year: 1998 Country: Ireland Study design: Controlled cohort study Number of centres: Not reported Funding: Not reported	Tests: DNA tests (C282Y and H63D) Other interventions used: Control cohort: all HLA typed at the HLA-A, HLA-B and HLA DR loci	Number of participants: Haemochromatosis cohort: 30; control cohort: 404 Sample attrition/dropout: Not reported Sample crossovers: Not applicable Inclusion criteria for study entry: Haemochromatosis cohort: Clinically assessed and pathologically diagnosed by liver biopsy as having primary haemochromatosis Control cohort: Not specified but were all volunteers from a bone marrow registry Exclusion criteria for study entry: Not reported Characteristics of participants: Not reported	Primary outcome: Prevalence of C282Y and H63D *HFE* genotypes in patient and control cohorts Secondary outcomes: Linkage disequilibrium analysis of *HFE* gene mutations with the HLA-A, HLA-B and HLA-DR loci in the control cohort Method of assessing outcomes: Chromosomal DNA extracted from peripheral blood followed by PCR amplification of a 2224 base pair region of the *HFE* gene containing the positions where the mutations occur. Specificity of the reaction checked by sequencing PCR products derived from a number of samples. Mutation analysis carried out by immobilising PCR products on replicate nylon membranes and independently hybridising these with four digoxigenin-labelled oligonucleotide probes specific for the normal and mutant versions of the *HFE* sequence. Alkaline phosphatase-labelled antidigoxigenin antibody used to detect bound digoxigenin probes and reaction visualised by chemiluminescent detection, using CSPD substrate (Boehringer Mannheim). Samples of known *HFE* genotype always included to control and confirm the specificity of the probes used. HLA typing at the HLA-A and HLA-B locus using a medium PCR-SSOP typing scheme (reference given) and at the HLA-DR locus using a low resolution PCR-SSOP typing scheme (reference given) down to the allele or broad allele group Adverse symptoms: None reported Length of follow-up: No follow-up Recruitment dates: Not reported

Results

Primary outcomes	Haemochromatosis cohort ($n = 30$), n (%)	Control cohort ($n = 404$), n (%)
C282Y, C282Y	27 (90.0)	5 (1.24)
C282Y, wt	1 (3.3)	60 (14.85)
C282Y, H63D	0 (0)	10 (2.48)
H63D, H63D	1 (3.3)	6 (1.49)
H63D, wt	0 (0)	92 (22.77)
wt, wt	1 (3.3)	231 (57.18)

Comments: Original results also present 95% confidence intervals. The paper does not report on statistical differences between groups and no *p*-values are presented

C28Y homozygosity	**Iron overload population (defined)**		**Control population**		**Total**	
Yes, DNA test positive	a	27	b	5	a+b	32
No, DNA test negative	c	3	d	399	c+d	402
Total	a+c	30	b+d	404	a+b+c+d	434

Calculate clinical sensitivity, specificity, PPV and NPV if possible and note whether this agrees with any of these values that are reported in the text of the paper:

Clinical sensitivity = a/a + c = 27/30 × 100 = 90.0%

Clinical specificity = d/b + d = 399/404 × 100 = 98.8%

PPV = a/a + b = 27/32 × 100 = 84.4%

NPV = d/c + d = 399/402 × 100 = 99.3%

Comments:

Quality assessment by modified QUADAS[80] and Spitzer *et al.*[81]

Item		**Judgement[a]**
1.	Were selection criteria for eligibility of patients objective and clearly described?	U
2.	Is the definition of iron overload likely to correctly classify HHC?	U
3.	Did the study use proper sampling so that all patients were equally likely to enter the study?	U
4.	Was the control population appropriate?	N (no information)
5.	Did the study use proper sampling so that all control subjects were equally likely to enter the study?	N
6.	Was the DNA test described in sufficient detail to permit replication?	Y
7.	Was the execution of the biochemical methods described in sufficient detail to permit replication?	n/a
8.	Were the groups under comparison comparable in terms of age, sex and race?	U
9.	Was there any mention of missing data?	N
10.	Was the sample of patients representative of the patients who will receive the test in practice, i.e. are the results generalisable?	U

a Y, yes; N, no; U, unclear; n/a, not applicable.

Reference and design	Intervention	Participants	Outcome measures
Author: Neilsen *et al*.[92] Year: 1998 Country: Germany Study design: Cohort with control Number of centres: One Funding: Not stated	Tests: DNA tests (C282Y and H63D); serum iron to give serum ferritin (SF; μg/l), transferrin saturation (TS; %) and liver iron content (LIC)	Number of participants: HHC patients: 92 (unrelated); healthy volunteer control subjects: 157 (unrelated) (family members of patients: 34 – not reported here). All patients and control subjects of German ancestry (at least three generations) Sample attrition/dropout: None Sample crossovers: n/a Inclusion criteria for study entry: HHC patients: Presence of at least three of the following criteria: TS > 62%; SF > 300 μg/l; LIC > 2000 μgFe/g wet weight; hepatic iron index (HII) [HI (μg/year) = (LIC/age)] > 30; grade III or IV stainable iron in liver; > 4 g of iron removed by phlebotomy Family members: All relatives available Controls subjects: Unrelated healthy volunteers Exclusion criteria for study entry: None stated Characteristics of participants:* HHC patients: 92 (59 men, 33 women). Total: age 49.1±12.5, SF 1.087 (2.858–413), TS 90±11, LIC 2.16 (3.51–1.33). Men: age 48.7±12.6, SF 1451 (3.471–607), TS 96±11, LIC 2.22 (3.73–1.32). Women: age 49.6±12.6, SF 701 (1.721–286), TS 88±10, LIC 2.08 (3.21–1.35) Control subjects: 157 (80 men, 77 women). Total: age 42.3±17.1, SF 49 (138–17), TS 31±13, LIC not detected. Men: age 42.8±16.3, SF 75 (183–31), TS 33±11, LIC not detected. Women: age 41.8±17.8, SF 33 (90–12), TS 29±14, LIC not detected *Results for SF and LIC are geometric mean and asymmetric widths	Primary outcomes: Frequency of C282Y and H63D Secondary outcomes: Parameters of iron metabolism Method of assessing outcomes: Genomic DNA isolated from EDTA blood samples using QIAamp Blood Kit. PCR using primers for C282Y and H63D mutations. Amplified products digested with SnaBI for C282Y mutation and BclI for H63D mutation. SF, TS and total iron-binding capacity using routine methods. Liver iron measured non-invasively using SQUID biomagnetometer Adverse symptoms: n/a Length of follow-up: n/a Recruitment dates: 1993–7

Results

Genotypes	Patients (*n*=92)	Family members (*n*=34)	Control subjects (*n*=157)	*p*-value
Homozygosity C282Y	87	9	0	
Composite heterozygosity	4	3	NR	
Heterozygosity C282Y	1	18	15	
Homozygosity H63D	0	0	2	
Heterozygosity H63D	0	1	37	
No mutation	0	3	NR	

Comments: Unclear reporting in paper makes calculations for composite heterozygosity difficult

C28Y homozygosity	Iron overload population (defined)		Control population		Total	
Yes, DNA test positive	a	87	b	0	a+b	87
No, DNA test negative	c	5	d	157	c+d	162
Total	a+c	92	b+d	157	a+b+c+d	249

Calculate clinical sensitivity, specificity, PPV and NPV if possible and note whether this agrees with any of these values that are reported in the text of the paper:

Clinical sensitivity = a/a + c = 87/92 × 100 = 94.6%

Clinical specificity = d/b + d = 157/157 × 100 = 100%

PPV = a/a + b = 87/87 × 100 = 100%

NPV = d/c + d = 157/162 × 100 = 96.9%

Comments: Reported that 96.4% of patients were homozygous and 4.3% were heterozygous for C282Y

Quality assessment by modified QUADAS[80] and Spitzer *et al.*[81]

Item		Judgement[a]
1.	Were selection criteria for eligibility of patients objective and clearly described?	Y
2.	Is the definition of iron overload likely to correctly classify HHC?	Y
3.	Did the study use proper sampling so that all patients were equally likely to enter the study?	U
4.	Was the control population appropriate?	N
5.	Did the study use proper sampling so that all control subjects were equally likely to enter the study?	N
6.	Was the DNA test described in sufficient detail to permit replication?	Y
7.	Was the execution of the biochemical methods described in sufficient detail to permit replication?	N
8.	Were the groups under comparison comparable in terms of age, sex and race?	U
9.	Was there any mention of missing data?	N
10.	Was the sample of patients representative of the patients who will receive the test in practice, i.e. are the results generalisable?	Y

a Y, yes; N, no; U, unclear.

Reference and design	Intervention	Participants	Outcome measures
Author: Ryan *et al*[93] Year: 1998 Country: Ireland Study design: Cohort with control Number of centres: One Funding: Not stated	Tests: DNA tests (C282Y and H63D)	Number of participants: (1) HHC patients: 60 (unrelated); (2) HHC patients: 18 (lower iron overload); (3) unrelated controls: 109 Sample attrition/dropout: None Sample crossovers: n/a Inclusion criteria for study entry: (1) For HHC patients diagnosis on basis of clinical history, physical examination, persistently raised transferrin saturation and serum ferritin and > 3+ hepatic iron deposition; (2) HHC with persistently raised iron indices but < 3+ hepatic iron deposition on liver biopsy; (3) control group of randomly selected individuals from hospital staff Exclusion criteria for study entry: None stated Characteristics of participants: Not stated	Primary outcome: Frequency of C282Y and H63D Secondary outcomes: Parameters of iron metabolism Method of assessing outcomes: DNA extracted from 10µl blood collected in EDTA tubes or from Guthrie cards using Chelex resin. Primers used to amplify fragments of C282Y and H63D included internal restriction enzyme control sites. Following amplification the PCR product was digested with RsaI for C282Y mutation and MboI for H63D mutation. No details of biochemical tests Adverse symptoms: n/a Length of follow-up: n/a Recruitment dates: Not stated

Results

Genotypes	Group 1: HII > 3+, *n*	Group 2: HII < 3+, *n*	Group 3: Control group, *n*
Homozygosity C282Y	56	14	0
Composite heterozygosity	1	2	
Heterozygosity C282Y	1	1	31
Homozygosity H63D	ND		4
Heterozygosity H63D	ND	1	27
No mutation	2	0	47

Comments: ND, not determined because of complete linkage disequilibrium

C28Y homozygosity	Iron overload population (defined): Group 1: HII > 3+		Control population		Total	
Yes, DNA test positive	a	56	b	0	a+b	56
No, DNA test negative	c	4	d	109	c+d	113
Total	a+c	60	b+d	109	a+b+c+d	169

Calculate clinical sensitivity, specificity, PPV and NPV if possible and note whether this agrees with any of these values that are reported in the text of the paper:

Clinical sensitivity = a/a + c = 56/60 × 100 = 93.3%

Clinical specificity = d/b + d = 109/109 × 100 = 100%

PPV = a/a + b = 56/56 × 100 = 100%

NPV = d/c + d = 109/113 × 100 = 96.5%

Comments: Reported that 93% of HHC patients fulfilling standard diagnostic criteria are homozygous for C282Y

C28Y homozygosity	**Iron overload population (defined): Group 2: HII < 3+**		**Control population**		**Total**	
Yes, DNA test positive	a	14	b	0	a+b	14
No, DNA test negative	c	4	d	109	c+d	113
Total	a+c	18	b+d	109	a+b+c+d	127

Calculate clinical sensitivity, specificity, PPV and NPV if possible and note whether this agrees with any of these values that are reported in the text of the paper:

Clinical sensitivity = a/a + c = 14/18 × 100 = 77.8%

Clinical specificity = d/b + d = 109/109 × 100 = 100%

PPV = a/a + b = 14/14 × 100 = 100%

NPV = d/c + d = 109/113 × 100 = 96.5%

Comments: Reported that 77% of patients with provisional diagnoses of HHC but who do not fulfil standard diagnostic criteria are homozygous for C282Y mutation

Quality assessment by modified QUADAS[80] and Spitzer et al.[81]

Item		**Judgement[a]**
1.	Were selection criteria for eligibility of patients objective and clearly described?	U
2.	Is the definition of iron overload likely to correctly classify HHC?	U
3.	Did the study use proper sampling so that all patients were equally likely to enter the study?	U
4.	Was the control population appropriate?	N
5.	Did the study use proper sampling so that all control subjects were equally likely to enter the study?	Y
6.	Was the DNA test described in sufficient detail to permit replication?	Y
7.	Was the execution of the biochemical methods described in sufficient detail to permit replication?	N
8.	Were the groups under comparison comparable in terms of age, sex and race?	U
9.	Was there any mention of missing data?	N
10.	Was the sample of patients representative of the patients who will receive the test in practice, i.e. are the results generalisable?	U

a Y, yes; N, no; U, unclear.

Reference and design	Intervention	Participants	Outcome measures
Author: UK Haemochromatosis Consortium[38] Year: 1997 Country: UK Study design: Cohort with control Number of centres: Four Funding: NE Thames Regional Health Authority, Peter Samuel Charitable Trust, Nuffield Foundation	Tests: DNA tests (C282Y and H63D)	Number of participants: 115 well-characterised patients with HHC; control group: 101 healthy blood donors Sample attrition/dropout: None Sample crossovers: n/a Inclusion criteria for study entry: Diagnosis of HHC on the basis of hepatic iron index > 1.9 or greater than 5 g mobilisable iron by quantitative phlebotomy. Control samples were obtained from healthy blood donors Exclusion criteria for study entry: None stated Characteristics of participants: Not stated	Primary outcome: Frequency of C282Y and H63D Secondary outcomes: Method of assessing outcomes: The prevalence of the C282Y and H63D mutations was determined by PCR amplification and restriction enzyme digestion Adverse symptoms: n/a Length of follow-up: n/a Recruitment dates: Not stated

Results

Primary outcomes	Intervention group, *n*	Control group, *n*	
HH/YY	105	1	Homozygous
HH/CC	5	65	Wild type
HD/CC	0	22	
HD/CY	3	4	
HH/CY	1	6	
DD/CC	1	3	

Comments:

C28Y homozygosity	Iron overload population (defined)		Control population		Total	
Yes, DNA test positive	a	105	b	1	a+b	106
No, DNA test negative	c	10	d	100	c+d	110
Total	a+c	115	b+d	101	a+b+c+d	216

Calculate clinical sensitivity, specificity, PPV and NPV if possible and note whether this agrees with any of these values that are reported in the text of the paper:

Clinical sensitivity = a/a + c = 105/115 × 100 = 91.3%

Clinical specificity = d/b + d = 100/101 × 100 = 99.0%

PPV = a/a + b = 105/106 × 100 = 99.0%

NPV = d/c + d = 100/110 × 100 = 91.0%

Comments: Reported that 91% of patients with HHC were homozygous for the C282Y mutation

Quality assessment by modified QUADAS[80] and Spitzer *et al.*[81]

Item		Judgement[a]
1.	Were selection criteria for eligibility of patients objective and clearly described?	Y
2.	Is the definition of iron overload likely to correctly classify HHC?	Y
3.	Did the study use proper sampling so that all patients were equally likely to enter the study?	U
4.	Was the control population appropriate?	U
5.	Did the study use proper sampling so that all control subjects were equally likely to enter the study?	U
6.	Was the DNA test described in sufficient detail to permit replication?	Y
7.	Was the execution of the biochemical methods described in sufficient detail to permit replication?	N
8.	Were the groups under comparison comparable in terms of age, sex and race?	U
9.	Was there any mention of missing data?	N
10.	Was the sample of patients representative of the patients who will receive the test in practice, i.e. are the results generalisable?	Y

a Y, yes; N, no; U, unclear.

Reference and design	Intervention	Participants	Outcome measures
Author: Vantyghem *et al.*[94] Year: 2006 Country: France Study design: Cohort with control Number of centres: One Funding: Not stated	Tests: DNA tests (C282Y and H63D)	Number of participants: I group patients: 156 recruited at endocrinology department; C group control subjects: 106 Sample attrition/dropout: None Sample crossovers: n/a Inclusion criteria for study entry: I group: Abnormal iron markers, serum ferritin (SF) > 300 ng/ml or transferrin saturation (TS) > 45%. Tests performed because of general symptoms (fatigue, weight loss, arthralgia), diabetes, hepatomegaly, disturbed liver enzymes or hypogonadism C group: Healthy Caucasian subjects without family history of diabetes or iron overload Exclusion criteria for study entry: None stated Characteristics of participants:* I group: 68% men, age 52±17 years, body mass index 27±6 kg/m^2, blood iron level 145±56 µg/dl, SF 910±1304 ng/ml, TS 58±28%. Clinical symptoms: 11% melanodermic, 51% diabetic, 24% admitted excessive alcohol intake, 26% had hepatomegaly, 10% complained of arthralgia, 10% suffered from heart disease C group: No details given * Data are mean±SD	Primary outcome: Frequency of C282Y and H63D Secondary outcomes: Parameters of iron metabolism Method of assessing outcomes: DNA extracted from whole blood samples. *HFE* mutations were detected with PCR assays followed by restriction enzyme digestion with Rsa1 for C282Y and Bcl1 for H63D. Blood samples for iron parameters collected from fasting patients. Serum iron levels were measured using standard colorimetric method, and serum transferrin levels were determined by rate immunoturidimetry on an automated analyser. Serum TS values were calculated as follows: [(serum iron/2) x SF)] × 100. SF levels were measured by chemiluminescence immunoassay Adverse symptoms: n/a Length of follow-up: n/a Recruitment dates: Not stated

Results						
Genotypes	**Group I (abnormal iron parameters) (*n* = 156), *n* (%)**		**Group C (control) (*n* = 106), *n* (%)**		**χ^2 *p*-value < 0.001, I vs C**	
Homozygosity C282Y	33 (21)		0			
Composite heterozygosity	10 (6.4)		2 (1.8)			
Heterozygosity C282Y	34 (21)		14 (13.2)			
Homozygosity H63D	5 (3.2)		7 (6.6)			
Heterozygosity H63D	33 (21)		23 (21.6)			
No mutation	41 (26)		60 (57)			
C28Y homozygosity	**Iron overload population (defined): Group I**		**Group C (control)**		**Total**	
Yes, DNA test positive	a	33	b	0	a+b	33
No, DNA test negative	c	123	d	106	c+d	229
Total	a+c	156	b+d	106	a+b+c+d	262

Calculate clinical sensitivity, specificity, PPV and NPV if possible and note whether this agrees with any of these values that are reported in the text of the paper:

Clinical sensitivity = a/a + c = 33/156 × 100 = 21.2%

Clinical specificity = d/b + d = 106/106 × 100 = 100%

PPV = a/a + b = 33/33 × 100 = 100%

NPV = d/c + d = 106/229 × 100 = 46.3%

Comments:

Quality assessment by modified QUADAS[80] and Spitzer *et al*.[81]

Item		**Judgement[a]**
1.	Were selection criteria for eligibility of patients objective and clearly described?	Y
2.	Is the definition of iron overload likely to correctly classify HHC?	U
3.	Did the study use proper sampling so that all patients were equally likely to enter the study?	U
4.	Was the control population appropriate?	Y
5.	Did the study use proper sampling so that all control subjects were equally likely to enter the study?	U
6.	Was the DNA test described in sufficient detail to permit replication?	N
7.	Was the execution of the biochemical methods described in sufficient detail to permit replication?	U
8.	Were the groups under comparison comparable in terms of age, sex and race?	U
9.	Was there any mention of missing data?	N
10.	Was the sample of patients representative of the patients who will receive the test in practice, i.e. are the results generalisable?	U

a Y, yes; N, no; U, unclear.

Reference and design	Intervention	Participants	Outcome measures
Author: Willis *et al*.[95] Year: 1997 Country: UK Study design: Cohort with control Number of centres: One Funding: Not stated	Tests: DNA tests (C282Y and H63D)	Number of participants: Patients: 18; control subjects: 200 Sample attrition/dropout: None Sample crossovers: n/a Inclusion criteria for study entry: Patients being treated for HHC by phlebotomy. Criteria were fasting transferrin saturation > 60% in two samples and hepatic iron index > 2 where appropriate Control subjects were patients referred to hospital for reasons unrelated to known manifestations of HHC representative of hospital population; different patient groups were included Exclusion criteria for study entry: None stated Characteristics of participants: Not stated	Primary outcome: Frequency of mutant alleles, 845A (C282Y) and 187G (H63D) Secondary outcomes: Method of assessing outcomes: DNA was extracted by standard methods from blood and amplified in PCR reactions. PCR products underwent allelle-specific oligonucleotide hybridisation for wild type and mutant nucleotide 845 alleles. For nucleotide 187 alleles PCR product restriction digestion with Bcl1 was performed (full details given) Adverse symptoms: n/a Length of follow-up: n/a Recruitment dates: Not stated

Results

Genotypes	Patients ($n = 18$)	Controls ($n = 200$)
Homozygosity C282Y	18	1
Composite heterozygosity		
Heterozygosity C282Y		32
Homozygosity H63D		
Heterozygosity H63D		
Normal homozygous H63D	18	
No mutation		
Comment: Full results not reported		

C28Y homozygosity	Iron overload population (defined) ($n = 18$)		Control population ($n = 200$)		Total	
Yes, DNA test positive	a	18	b	1	a+b	19
No, DNA test negative	c	0	d	199	c+d	199
Total	a+c	18	b+d	200	a+b+c+d	218

Calculate clinical sensitivity, specificity, PPV and NPV if possible and note whether this agrees with any of these values that are reported in the text of the paper:

Clinical sensitivity = a/a + c = 18/18 × 100 = 100%

Clinical specificity = d/b + d = 199/200 × 100 = 99.5%

PPV = a/a + b = 18/19 × 100 = 94.7%

NPV = d/c + d = 199/199 × 100 = 100%

Comments:

Quality assessment by modified QUADAS[80] and Spitzer *et al*.[81]		
Item		**Judgement**[a]
1.	Were selection criteria for eligibility of patients objective and clearly described?	Y
2.	Is the definition of iron overload likely to correctly classify HHC?	Y
3.	Did the study use proper sampling so that all patients were equally likely to enter the study?	U
4.	Was the control population appropriate?	N
5.	Did the study use proper sampling so that all control subjects were equally likely to enter the study?	U
6.	Was the DNA test described in sufficient detail to permit replication?	Y
7.	Was the execution of the biochemical methods described in sufficient detail to permit replication?	n/a
8.	Were the groups under comparison comparable in terms of age, sex and race?	U
9.	Was there any mention of missing data?	N
10.	Was the sample of patients representative of the patients who will receive the test in practice, i.e. are the results generalisable?	Y

a Y, yes; N, no; U, unclear; n/a, not applicable.

Appendix 8

Data extraction of psychosocial studies

Reference and design	Intervention	Participants	Outcome measures
Author: Hicken *et al.*[96] Year: 2004 Country: USA Study design: Cohort with control Number of centres: One Funding: Not reported	Haemochromatosis cohort: Haemochromatosis interview with additional questions Control cohort: Haemochromatosis interview Other interventions used: None	Number of participants: Haemochromatosis cohort: 87; control cohort: 50 Sample attrition/dropout: Interviews with 10 patients were pilot data and were included only in analyses of outcomes and attitudes about genetic testing Sample crossovers: None Inclusion criteria for study entry: Haemochromatosis cohort: (1) Caucasians aged > 18 years; (2) had haemochromatosis; (3) underwent phlebotomy to reduce or maintain ferritin levels between January 1990 and May 2000; (4) underwent *HFE* genotyping at least 1 year before chart review Control cohort: People with hypertension enrolled in a trial of an antihypertensive medication. Eligible control subjects: (1) were Caucasians aged > 18 years; (2) reported that they did not have haemochromatosis; (3) had not undergone *HFE* genotyping Exclusion criteria for study entry: None reported Characteristics of participants: Haemochromatosis cohort: Age (mean±SD) 53.9±12.5 years (range 25–82); years between *HFE* genotyping and study 2.7±1.7 (1.7–4.9); male–female 55%:45%; married 82%, single/divorced/widowed 18%; employed 59%, unemployed/retired 41%; annual income US$0–50,000 47%, US$50,001–75,000 46%, income data missing 7%; education < high school 8%, high-school graduate 22%, post high school 61%, education data missing 9%; health insurance 98%, no health insurance 2% Control cohort: Age (mean±SD) 58.5±13.7 years (range 31–80); years between *HFE* genotyping and study n/a; male–female 56%:44%; married 58%, single/divorced/widowed 42%; employed 50%, unemployed/retired 50%; annual income US$0–50,000 62%, US$50,001–75,000 36%, income data missing 2%; education < high school 12%, high-school graduate 22%, post high school 66%, health insurance 82%, no health insurance 14%, missing/don't know 4%	Primary outcome: Knowledge questions answered correctly Secondary outcomes: Attitudes about genetic testing; psychosocial outcomes of genetic testing. For haemochromatosis cohort only, compliance with treatment, understanding of haemochromatosis and treatment, psychosocial outcomes of *HFE* genotyping Method of assessing outcomes: Two independent raters categorised short-answer questions using a reliable coding system, discussed discrepant rating and agreed upon a code that matched the response. Short-answer knowledge questions were scored as either correct or incorrect. Summary scores for outcomes of genetic testing were created by summing positive outcomes (score range 4–16) and negative outcomes (score range 8–32) of genetic testing Adverse symptoms: n/a Length of follow-up: n/a Recruitment dates: n/a

Results			
Outcome	**Haemochromatosis cohort ($n = 57$)**	**Control cohort ($n = 50$)**	***p*-value**
HFE genotyping beneficial	12.44	13.14	> 0.05
HFE genotyping detrimental	17.56	13.39	< 0.0001
Comments: 34% of patients ($n = 30$) did not recall undergoing *HFE* genotyping and were not included in the analyses			
Control subjects expected more anxiety ($p < 0.0001$), sadness ($p < 0.0001$) and anger ($p < 0.005$), and to have more difficulty paying for genetic testing ($p < 0.0001$) than was reported by patients (results reported in bar chart)			
Summary scores for positive outcomes range from 4 to16 and for negative outcomes from 8 to 32			

Outcome: Compliance with treatment	**Haemochromatosis cohort ($n = 87$)**	**Control cohort ($n = 50$)**	***p*-value**
Achieved iron depletion	99%	n/a	
Adherence to maintenance therapy in first year	94%	n/a	
Few difficulties obtaining annual serum ferritin measurements	81%	n/a	
Comments: Adherence to maintenance therapy declined by 8% annually after the first year. Demographic factors, barriers and knowledge were not associated with adherence to maintenance ($p > 0.05$)			

Outcome	**Haemochromatosis cohort ($n = 57$)**	**Control cohort ($n = 50$)**	***p*-value**
Satisfied with information received before genotyping (mean ± SD)	3.39 ± 0.59 (range 2–4)		
Test determines presence of *HFE* mutation	46%		
Test confirms diagnosis of haemochromatosis	11%		
Do not recall	18%		
Wanted to receive the test (mean ± SD)	3.38 ± 0.56 (range 2–4)		
Understood the rationale for the testing (mean ± SD)	3.38 ± 0.59 (range 2–4)		

Questions			
Individual knowledge questions	**Patients ($n = 87$), correct recall (%)**	**Control subjects ($n = 50$), correct recall (%)**	***p*-value**
Overall recall	65 ± 26	59 ± 30	> 0.05
Define genetic test	48	56	
Interpret positive HFE genotype	59	62	
Immutability of genetic test result	65	64	
Phlebotomy changes iron levels	81	86	
Test predicts symptoms	51	42	
Test indicates current illness	45	36	
Test predicts when symptoms begin	75	76	
Children and siblings will have same mutation	49	52	

Short-answer questions	**% Patients with correct answer**
Purpose of phlebotomy	85
Purpose of annual serum ferritin measurement	79
Definition of genetic	90
Difference between *HFE* genotyping and transferrin saturation test	25
True–false questions	**% Patients with correct answer**
In haemochromatosis the body tends to store too much iron	98
No effective treatment for haemochromatosis	92
Haemochromatosis treated by drawing blood to lower iron levels	98
Not necessary to treat haemochromatosis unless the person has organ damage	96
Possible to have haemochromatosis and not know it	99
About 1 out of every 200 people has haemochromatosis	60
People with haemochromatosis get sick because too much iron damages organs	97
Untreated haemochromatosis may lead to early death	97
No cure for haemochromatosis	86
Haemochromatosis is less common in women	42
Perceived benefits (haemochromatosis cohort* n=*57)	
Improved health and prevention of future health problems	40%
Learning risk to self and family	19%
Improved understanding of health	11%
Improved psychological well-being	12%
No benefits from *HFE* genotyping identified	19% (*n* = 11)
Problems from genetic testing (haemochromatosis cohort* n=*57)	
No problems identified	88% (*n* = 49)
Decreased psychological well-being	2% (*n* = 1)
Denied health insurance	2% (*n* = 1)
Comments:	
Methodological comments	
Allocation to treatment groups:	
Blinding: Not reported	
Comparability of treatment groups: Some significant differences with respect to marital status and health insurance	
Method of data analysis:	
Sample size/power calculation: Not reported	
Attrition/dropout: Well reported	
General comments	
Generalisability:	
Outcome measures:	
Intercentre variability: Not applicable	
Conflict of interests: Not reported	

Quality assessment						
	Yes	**U/I/S[a]**	**No**	**DK/NR[b]**	***n*/a[c]**	**Comments**
Proper random assignment					n/a	
Proper sampling				NR		
Adequate sample size				NR		
Objective outcomes	Y					
Blind assessment				NR		
Objective eligibility criteria	Y					
Reported attrition	Y					
Comparability of groups			N			
Generalisability		U				

a U/I/S, uncertain/incomplete/substandard.
b DK/NR, don't know/not reported.
c n/a, not applicable.
Quality criteria for assessment of observational studies revised from Spitzer *et al*.[81]

Reference and design	Intervention	Participants	Outcome measures
Author: Meiser *et al*.[97] Year: 2005 Country: Australia Study design: Cohort without control Number of centres: One Funding: Author supported by National Health and Medical Research Council of Australia	Self administered questionnaires: genetics of haemochromatosis knowledge (at 2 weeks and 12 months post consultation); understanding of test result (at 2 weeks post consultation only); 7-item intrusion subscale of the Impact of Event Scale (IES) (at 2 weeks post consultation only); 6-item short version of the state component of the State–Trait Anxiety Inventory (STAI-State); Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) Other interventions used: None	Number of participants: Haemochromatosis cohort: 101 Sample attrition/dropout: Participants were lost to follow-up: 74 (73.3%) and 62 (61.4%) completed the 2-week and 12-month post-consultation questionnaires respectively. There are four, five or six missing baseline data points for each of the reported clinical variables Sample crossovers: None Inclusion criteria for study entry: Recruited through a haemochromatosis clinic at a major teaching hospital. Participants referred for diagnostic evaluation of symptoms, genetic testing for HHC, advice regarding early detection and preventative strategies and/or standardised patient education tailored to individual needs Exclusion criteria for study entry: Unable to give informed consent or had limited literacy in English Characteristics of participants, *n* (%): Age < 30 years 16 (15.8), 30–39 years 17 (16.8), 40–49 years 22 (21.8), 50–59 years 37 (36.6), 60+ years 9 (8.9), mean age 45 years (range 18–69); male 63 (62.4), female 38 (37.6); married 73 (72.3), not married 28 (27.7); biological children 72 (71.3), no biological children 29 (28.7); post-school qualifications 77 (65.3), no post-school qualifications 24 (23.8); clinically unaffected 66 (68.8), clinically affected 30 (31.3); ferritin level low 13 (13.7), ferritin level high 82 (86.3); mutation status – homozygous for C282Y 43 (45.3), homozygous for H63D 11 (11.6), compound heterozygote (C282Y/H63D) 20 (21.1), heterozygote C282Y 13 (13.7), heterozygote H63D 8 (8.4); family history of haemochromatosis 48 (47.5), no family history 49 (48.5)	Primary outcomes: Psychological distress levels (IES, STAI-State and SF-36) Secondary outcomes: Knowledge about genetics of haemochromatosis and understanding of test results Method of assessing outcomes: Intrusion subscale of the IES: scale ranges from 'not at all' to 'often'. STAI-State scale ranges from 'not at all' to 'very much', scores range from 20 to 80. SF-36 provides indicators across eight dimensions, scores for each range from 0 to 100, with higher scores indicating better health or well-being. There are two summary indices, the physical component summary (PCS) and the mental component summary (MCS). General US population averages are exactly 50 for both SF-36 component summaries, the standard deviation is 10 for both the PCS and the MCS Adverse symptoms: N/A Length of follow-up: 12 months. Recruitment dates: February 2001–May 2003

Results				
Outcome	**Unaffected, mean (SD)**	**Affected, mean (SD)**	**Total, mean (SD)**	***p*-value**
STAI-State short version intrusion subscale baseline	45.8 (7.6), *n* = 59	45.5 (8.6), *n* = 26	45.8 (7.7), *n* = 89	0.89
STAI-State intrusion subscale 2 weeks post consultation	44.6 (7.1), *n* = 38	46.5 (7.1), *n* = 18	45.1 (7.0), *n* = 58	0.37
STAI-State intrusion subscale 12 months post consultation	43.2 (5.9), *n* = 21	44.6 (5.1), *n* = 16	43.8 (5.6), *n* = 37	0.45
Comments: *p*-value refers to a statistical comparison between mean scores of clinically affected and unaffected participants. Changes across time points for the STAI-State for both clinically unaffected and affected participants combined were not suggested by the data and this was confirmed by statistical analyses. There were no statistically significant associations between baseline generalised anxiety and age, sex, educational level, marital status or ferritin levels				
IES 2 weeks post consultation	4.0 (5.8), *n* = 44	5.6 (6.8), *n* = 21	4.6 (6.2), *n* = 68	0.48
Comments: *p*-value refers to a statistical comparison between mean scores of clinically affected and unaffected participants. One participant scored over 20 on the intrusion subscale of the IES. A score of 20 or higher on the intrusion subscale of the IES is considered to be strongly predictive of a significant stress response syndrome				
PCS of SF-36 baseline	49.0 (7.7), *n* = 59	42.9 (10.7), *n* = 28	46.9 (9.4), *n* = 91	0.02*
PCS of SF-36 2 weeks post consultation	47.8 (9.4), *n* = 42	43.6 (10.0), *n* = 20	46.4 (9.7), *n* = 65	0.06
PCS of SF-36 12 months post consultation	45.1 (11.5), *n* = 23	41.1 (14.0), *n* = 17	43.4 (12.6), *n* = 40	0.50
MCS of SF-36 baseline	46.7 (9.7), *n* = 59	42.3 (10.5), *n* = 28	45.3 (10.0), *n* = 91	0.06
MCS of SF-36 2 weeks post consultation	47.2 (9.8), *n* = 42	42.5 (12.0), *n* = 20	45.6 (10.6), *n* = 65	0.17
MCS of SF-36 12 months post consultation	51.0 (8.5), *n* = 23	45.7 (9.6), *n* = 17	48.7 (9.3), *n* = 40	0.08
Comments: *p*-value refers to a statistical comparison between mean scores of clinically affected and unaffected participants. *Significant at $p < 0.05$. Changes across time points for the PCS for both clinically unaffected and affected participants combined were not suggested by the data and this was confirmed by statistical analyses. Paper states that a statistically significant increase in the MCS score (i.e. better mental health) was observed at the 12-month follow-up compared with baseline (no *p*-value reported)				
For all indices of the SF-36 subscales clinically unaffected individuals had higher scores than affected individuals and these differences were statistically significant for most subscales: role–physical ($p < 0.001$), bodily pain ($p = 0.039$), general health ($p = 0.01$), vitality ($p = 0.01$), social functioning ($p = 0.017$) and mental health ($p = 0.02$). A trend for differences between clinically unaffected and affected participants was observed for role–emotional ($p = 0.092$), and no statistically significant differences were found for physical functioning ($p = 0.02$). There were no statistically significant associations between baseline PCS or baseline MCS and age, sex, educational level, marital status or ferritin levels				

Participants (*n* = 101) correctly answering:	**2-week follow-up (**estimated from figure)**	**12-month follow-up (all estimated values)**
Regular removal of blood will avoid or reduce many of the symptoms of haemochromatosis (True)	93.2%	98.7%
A person who has two copies of the gene change for haemochromatosis is likely to develop haemochromatosis (True)	87.3%	87.2%
Hereditary haemochromatosis is uncommon (False)	85.3%**	75.6%
A person who has just one copy of the gene change for haemochromatosis usually will be perfectly healthy (True)	76.1%	70.5%
To be at risk of developing haemochromatosis you need to inherit one copy of the gene change from each of your parents (True)	71.2%**	69.9%

If a person carried two copies of the haemochromatosis gene change they have a 100% change of passing on the two gene changes to a son or daughter (False)	54.5%**	67.9%
The gene change C282Y is found in most people with haemochromatosis (True)	45.2%	59.6%

Understanding of gene changes	**Participants (*n*=42) homozygous for C282Y or H63D, *n* (%)**	**Participants (*n*=19) heterozygous for C282Y or H63D, *n* (%)**	**Participants (*n*=16) compound heterozygotes, *n* (%)**
One gene change	7 (16.7)	12 (63.2)	4 (23.5)
Two gene changes	28 (66.7)	3 (15.8)	10 (58.8)
Unable to remember	7 (16.7)	4 (21.1)	2 (17.6)
Iron studies			
Uptake of iron studies	96% of participants for whom iron studies were recommended reported having had iron studies in the past year at the 12-month follow up		
Venesection	62% of participants who had increased serum ferritin at baseline reported ever having had a venesection; 57% reported having undergone a venesection in the past year		
Methodological comments			
Allocation to treatment groups: n/a			
Blinding: Not reported			
Comparability of treatment groups: n/a			
Method of data analysis:			
Sample size/power calculation: Not reported			
Attrition/dropout: Data is missing from some tables but this is not commented on by the authors. Loss to follow-up at 2 weeks and 12 months is reported with some information about the characteristics of the missing participants			
General comments			
Generalisability: Uncertain			
Outcome measures: Used validated instruments			
Intercentre variability: n/a			
Conflict of interests: Not reported			

Quality assessment						
	Yes	**U/I/S[a]**	**No**	**DK/NR[b]**	**n/a[c]**	**Comments**
Proper random assignment					n/a	
Proper sampling				NR		
Adequate sample size				NR		
Objective outcomes	Y					
Blind assessment				NR		
Objective eligibility criteria		U				
Reported attrition		I				
Comparability of groups					n/a	
Generalisability		U				

a U/I/S, uncertain/incomplete/substandard.
b DK/NR, don't know/not reported.
c n/a, not applicable.
Quality criteria for assessment of observational studies revised from Spitzer *et al*.[81]

Reference and design	Intervention	Participants	Outcome measures
Author: Power and Adams[98] Year: 2001 Country: Canada Study design: Observational before and after Number of centres: One Funding: Medical Research Council of Canada	Intervention: Genetic test; no control group Other interventions used: None	Number of participants: Participants drawn from two sources: (1) referred group: 117 patients being assessed for haemochromatosis – includes those suspected clinically and family members; (2) screened group: 25 homozygotes identified through a screening study – they were not aware of result. Control: n/a Sample attrition/dropout: Not reported although data does not appear to be complete in some analyses Sample crossovers: None Inclusion criteria for study entry: (1) Referred group: referred to clinic with suspicious clinical signs and symptoms, raised iron parameters, family history; (2) screened group: homozygotes identified as part of screening study Exclusion criteria for study entry: Not reported Characteristics of participants: 46 participants homozygous – 21 men, 25 women; 41 participants heterozygous – 18 men 23 women; remainder wild type, gender not reported. Mean age: referred group 46±13 years, screened group 41±12 years. Most of the referred group had raised ferritin and some had symptoms of possible haemochromatosis. All of the screened group were asymptomatic, three had raised ferritin	Primary outcomes: STAI-State Anxiety pre and post genetic test result; SF-36 pre and post genetic test result; 1-year post-genetic test result, screened group only: feelings about test results, questions assessing specific psychosocial outcomes Method of assessing outcomes: Pre test and immediately post test, standardised questionnaires administered; 1-year post-test structured interview (screened group only) Length of follow-up: 1 year post test for screened group only Recruitment dates: Not given

Results			
Primary outcomes	**Pre**	**Post**	***p*-value**
Mean STAI			
Overall ($n = 142$)	39.15 ± 11.45	35.54 ± 11.46	< 0.01
Homozygotes ($n = 27$)	39.7	34.0*	< 0.05*
Heterozygotes ($n = 23$)	37.2	32.2*	< 0.05*
Wild type ($n = 35$)	40.4	38.8	Not significant
Comments: Values for homozygotes, heterozygotes and wild-type subgroups read from chart. **p*-value for comparison with pretest value. These results include data from the 25 participants identified by population screening who do not meet the inclusion criteria of this review. *n* in subgroup analyses to not add up to the overall total			
SF-36			Overall no change
Vitality		Improvement	< 0.05
Comments: SF-36 scores reported in chart; too small to enable values to be read with any accuracy			
Methodological comments			
Allocation to treatment groups: n/a			
Blinding: n/a			
Comparability of treatment groups: n/a			
Method of data analysis: Seems appropriate			
Sample size/power calculation: n/a			
Attrition/dropout: Not reported			
General comments			
Generalisability: Screened population and referred population analysed together but no significant differences between the groups			
Outcome measures: Validated standardised measures used			
Intercentre variability: n/a			
Conflict of interests: None declared			

Quality assessment						
	Yes	**U/I/S[a]**	**No**	**DK/NR[b]**	**n/a[c]**	**Comments**
Proper random assignment					n/a	
Proper sampling				NR		
Adequate sample size						Sample size to determine if there was enough power to detect a difference not reported
Objective outcomes	Y					
Blind assessment				NR		
Objective eligibility criteria		U				
Reported attrition				NR		
Comparability of groups					n/a	
Generalisability		U				

a U/I/S, uncertain/incomplete/substandard.
b DK/NR, don't know/not reported.
c n/a, not applicable.
d The subgroup of 25 people identified by population screening do not meet the inclusion criteria of the review. Results for this group have not been reported on except where it is not possible to separate out these results from those of the referred patient group
Quality criteria for assessment of observational studies revised from Spitzer *et al*.[81]

Appendix 9

Data extraction of cost-effectiveness studies

Study characteristics		
Reference	Adams 1998[100]	El-Serag *et al*. 2000[99]
Country of origin	Canada	USA
Base year prices	1997	Studies from 1994 to 1999
Intervention	Screening with genetic test for haemochromatosis compared with using iron studies.	Screening with haemochromatosis-associated *HFE* gene testing compared with iron studies or no screening.
Study type	Cost-minimisation model	Cost-effectiveness decision tree model
Study group	Children and spouses of an affected proband with HHC; 291 children of 121 homozygotes	Hypothetical cohort of siblings and children of an affected proband with HHC
Perspective	Not stated (appears to be societal)	Societal
Industry role	None disclosed	Lead author supported by Glaxo Wellcome
Study base-case 'headline' predictions/ findings	Genotyping the spouse of a homozygote is the most cost-efficient strategy in pedigree studies	Gene testing is a cost-effective method of screening relatives of patients with HHC
Results		
Base case	The primary outcome was diagnosis of the C282Y mutation. Probands and children were also tested by phenotyping Of 121 homozygotes identified by phenotyping, 116 were homozygous for the C282Y mutation; 13 children out of 291 investigated were found with the C282Y mutation; 116 spouses were genotyped and 9 were found to be heterozygous for C282Y The costs incurred in the phenotypic strategy are the investigation of 291 children of homozygotes (CDN$58,200). The costs incurred in the spousal genotyping strategy are the investigation of 116 spouses and 22 subsequent children (CDN$35,600)	The outcome was estimated in life-years saved (LYS). The benefits were discounted at an annual rate of 3%. The discounted life expectancy was 39 years for children and 65.5 years for siblings The strategy of *HFE* gene testing of the proband, followed by testing of a child, was the most cost-effective strategy to screen one child at an incremental cost-effectiveness ratio (ICER) of US$508 per LYS. For screening two or more children the strategy of gene testing the spouse if the proband was found to be homozygous was the most cost-effective. For example, screening two children had an ICER of US$3665 per additional LYS, whereas screening using serum iron studies had an ICER of US$7934 per LYS and the strategy in which children were gene tested before the proband had an ICER of US$12,277 per LYS. For siblings, all screening strategies were dominant compared with no screening. Screening with serum iron studies was the most expensive screening strategy throughout. Of the two strategies that used *HFE* gene testing, gene testing of the siblings first resulted in lower costs when only one sibling was screened; however, for two or more siblings, *HFE* gene testing of the proband first was less costly

Sensitivity analysis	None reported	One-way and two-way sensitivity analyses were performed to measure the effect on the ICER, relative to no screening. The cost of gene testing was varied between US$191 and US$85. The cost of measuring serum iron transferrin saturation and serum ferritin was varied from US$85 to US$40. The proportion of patients with haemochromatosis in whom *HFE* gene testing was positive for the C282Y+/+ mutation was varied between 60% and 100%. The sensitivity and specificity of iron studies were varied between 90% and 100%. The frequency of serum iron studies in children was reduced to every 10 years. The prevalence of the C282Y+/– mutation in the population was varied between 1 per 1000 persons to 20 per 1000 persons
Conclusions		
	The genotyping of the spouse eliminated the need for the investigation of 269 children and resulted in a cost saving of 39%	*HFE* gene testing for the C282Y mutation was a cost-effective method for screening the relatives of patients with HHC
Caveats		
	There is some uncertainty in the reporting; 13 homozygotes were found amongst the 291 children but only 10 of these were genotyped. All children had normal transferrin saturation and ferritin; it is unclear how three of the homozygotes were identified The study assumes that the same number of people are diagnosed using either strategy and there will be the same benefit in each case. The sources of the costs are not reported. The study assumed that liver biopsy and venesection costs were similar between both strategies	The authors did not present sufficient detail to enable the appropriateness of the data sources to be discussed. Some of the authors' assumptions were not explicitly justified and no references were provided. The impact of some of the estimates was investigated by sensitivity analyses, but the ranges used were not adequately justified

Internal validity of economic evaluations

	Adams 1998[100]		**El Serag *et al*. 2000[99]**	
Item	**Critical appraisal**	**Reviewer comment**	**Critical appraisal**	**Reviewer comment**
Is there a well-defined question?	✓	Does genotyping of spouses of homozygotes result in fewer investigations of children and subsequent cost savings?	✓	To compare the cost-effectiveness of no screening with screening strategies that incorporate gene testing and serum iron studies for relatives of patients with confirmed HHC
Is there a clear description of alternatives (i.e. who did what to whom, where and how often)?	✓	All children of proband tested using biochemical and DNA tests vs all spouses tested using DNA tests and children of spouses, who are homozygous tested	✓	Genotypic vs iron studies vs no screening
Has the correct patient group/ population of interest been clearly stated?	✓	Children of an affected proband with HHC	✓	Siblings and children of an affected proband with HHC
Is the correct comparator used?	✓		✓	

Is the study type reasonable?	?	Cost-minimisation. The same number of children tested positive for C282Y mutation using both strategies	?	Cost-effectiveness analysis. No health-related quality of life values included
Is the perspective of the analysis clearly stated?	?		✓	Societal
Is the perspective employed appropriate?	?	Unclear how this relates to UK NHS	?	Unclear how this relates to UK NHS
Is the effectiveness of the intervention established?	✓		✓	
Has a lifetime horizon been used for analysis and if not has a shorter time horizon been justified?	✓		×	
Are the costs and consequences valued credibly?	?	Sources of costs not reported	?	The authors seem to have included all of the costs relevant to HHC and screening. The total costs were estimated using a decision model. The unit prices were derived from published studies and tariffs
Is differential timing considered?	✓		×	Costs discounted at 3%
Is incremental analysis performed?	✓		×	Cost per life-year saved
Is sensitivity analysis undertaken and presented clearly?	×	No	✓	Sensitivity analysis presented for cost of gene testing and iron studies, proportion of patients with HHC in whom gene testing was positive, sensitivity and specificity of iron studies and prevalence of C282 Y+/+ mutation in the population

External validity of economic studies

Item	Adams 1998[100]	El-Serag *et al.*2000[99]
1. Patient group – are the patients in the study similar to those of interest in England and Wales?	? Patient setting is from Canada	? Patient setting is from USA
2. Health-care system/setting – comparability to England and Wales; comparability of available alternatives; similar levels of resources; institutional arrangements comparable?	? Canadian perspective	? US perspective
3. Treatment – comparability with clinical management?	? Treatment in Canada although clinical management appears similar to that in UK	? Treatment in US although clinical management appears similar to that in UK
4. Resource costs – comparability between study and setting/population of interest?	× Canadian cost data	× US cost data

?, unclear or unknown; ✓, item judged suitable to generalise to England and Wales with or without some readjustment; ×, item judged not suitable to generalise to England and Wales as either not possible to see how an adjustment could be made easily in the short/medium term or relevant data unavailable.

Appendix 10
Systematic searches

Sensitivity and specificity of biochemical tests

Three studies[61,103,111] met the inclusion criteria for the systematic search and the results are reported in *Table 30*.

TABLE 30 *Sensitivity and specificity of biochemical tests*

Iron measurement	Sensitivity	Specificity	PPV	Reference
TS > 45%	94%	94%	6%	Olynyk *et al*. 1999[103]
TS > 50%	94%	96%	16%	Olynyk *et al*. 1999[103]
TS > 55%	90%			Adams and Chakrabarti 1998[111]
TS > 60%	91%	93%	31.3%	Moodie *et al*. 2002[61]
SF > 300 μg/l	96%			Adams and Chakrabarti 1998[111] (men)
	73%	85%	12.9%	Moodie *et al*. 2002[61]
	50%	87%	2%	Olynyk *et al*. 1999[103]
	75%	87%	2%	Olynyk *et al*. 1999[103]
SF > 200 μg/l	97%			Adams and Chakrabarti 1998[111] (women)
	73%	70%		Moodie[61]

PPV, positive predictive value; SF, serum ferritin; TS, transferrin saturation.

Liver biopsy complications

Two studies[124,125] met the inclusion criteria; however, these did not supply all of the data required and so the search was extended to include relevant audit studies that reported the necessary data (*Table 31*).

TABLE 31 *Liver biopsy complications*

	Probability	Reference	Comment
From randomised controlled trials			
Death	0%	Lindor *et al*. 1996[124]	
Bleeding (only bleeding, no mention of transfusion)	2.10%	Lindor *et al*. 1996[124]	With ultrasound
	4.40%	Lindor *et al*. 1996[124]	No ultrasound
	3.20%	Lindor *et al*. 1996[124]	Total
	2.40%	Papini *et al*.[126]	Menghini biopsy
	0.60%	Papini *et al*.[126]	Ultrasound
Extended inclusion criteria to find data for sensitivity analysis			

	Probability	Reference	Comment
Death	0.13–0.33%	Gilmore *et al*. 1995[119]	UK audit
	0–0.6%	Stone and Mayberry 1996[127]	UK audit
Bleeding requiring transfusion	0.7%	Gilmore *et al*. 1995[119]	UK audit
	1.8%	Stone and Mayberry 1996[127]	UK audit

Epidemiology

Results of the searches for epidemiology studies are reported in Chapter 1 (Epidemiology).

Appendix 11

Probabilistic sensitivity analysis

Parameters used for the probabilistic sensitivity analysis

Parameter name	Mean	Distribution	Alpha	Beta
Diagnostic pathway				
HHC prevalence	0.038	Beta	11	278.2
TS sensitivity	0.94	Triangle	0.75	0.99
TS specificity	0.94	Triangle	0.75	0.99
SF sensitivity	0.73	Triangle	0.5	0.99
SF specificity	0.85	Triangle	0.75	0.99
HHC DNA YY	0.913	Triangle	0.9	1
Proportion raised SF > 1000 μg/l				
DNA positive	0.39	Beta	11.9	18.7
DNA negative	0.24	Beta	26	82.4
Family testing, sibling				
Risk	0.25	Fixed		
Penetrance	0.76	Beta	20	6.3
SF > 200 μg/l, SF sensitivity	0.73	Triangle	0.5	0.99
SF > 200 μg/l, SF specificity	0.7	Triangle	0.5	0.99
Family testing, child				
Risk	0.05	Fixed		
Initial proportion with iron overload	0.2	Beta	12.1	48.4
Costs (£)				
DNA laboratory	100	Gamma	96.04	1.04
Nurse	8.75	Gamma	96.04	0.09
Consultant	39	Gamma	96.04	0.4
Liver biopsy	388.05	Gamma	96.04	4.04
Iron laboratory	23.40	Gamma	96.04	0.24
Venesection	8.75	Gamma	96.04	0.09
Number of monitors child	5	Gamma	24.01	0.2
Number of treatments	20	Gamma	61.46	0.32

SF, serum ferritin; TS, transferrin saturation; YY, homozygous C282Y/C282Y.

Results from the probabilistic sensitivity analysis

	Cost per case detected (£)		
	Diagnostic testing	**Family testing, sibling**	**Family testing, offspring**
First quartile	97	–234	7323
Second quartile	139	–189	8311
Third quartile	187	–145	9458
Fourth quartile	691	23	18,196

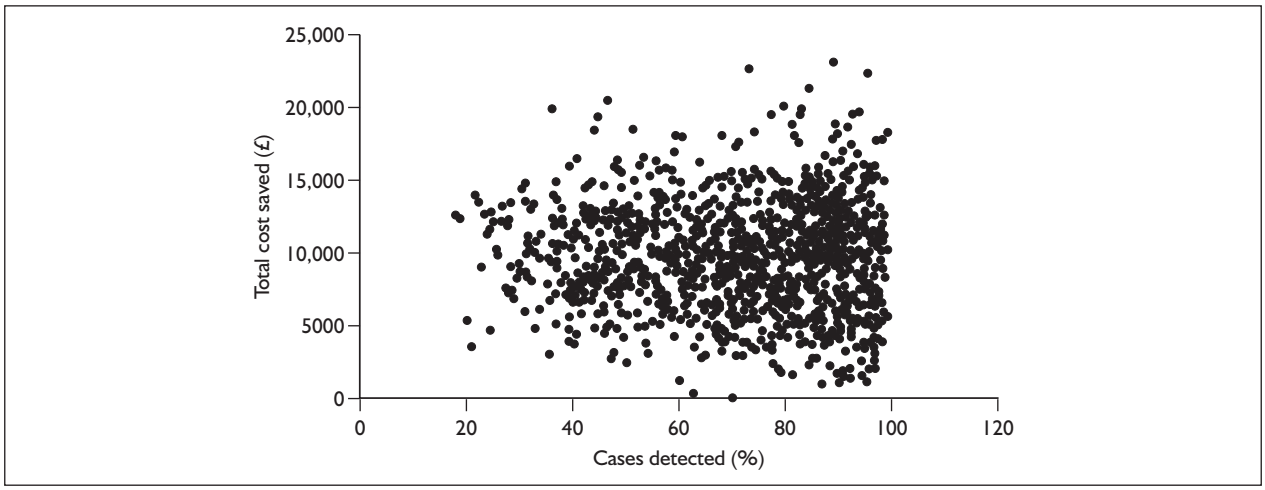

FIGURE 7 *Probabilistic sensitivity analysis results for cases detected and total costs saved for diagnostic testing decision tree.*

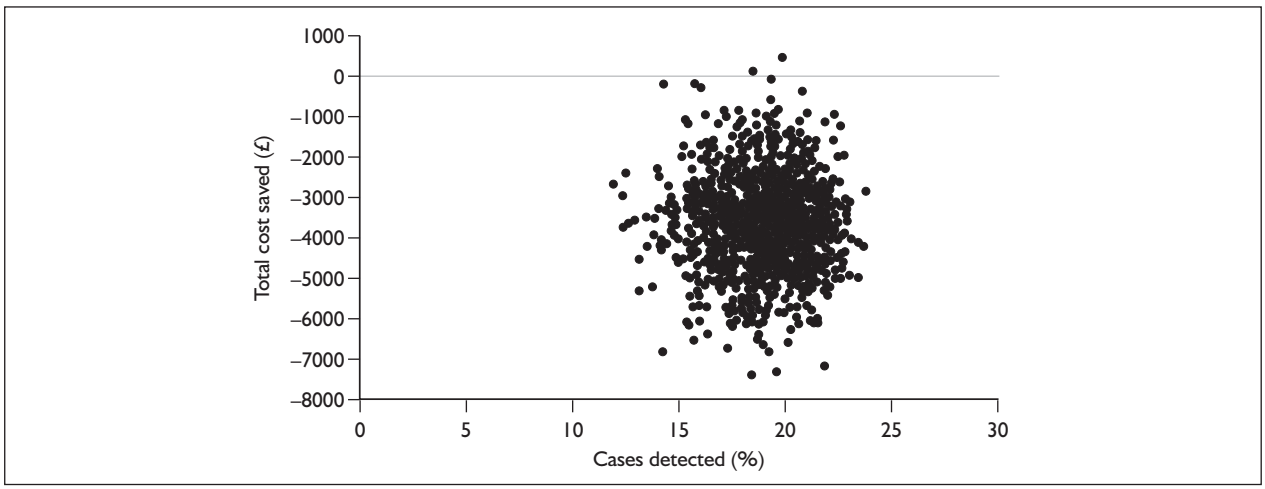

FIGURE 8 *Probabilistic sensitivity analysis results for cases detected and total costs saved for sibling family testing decision tree.*

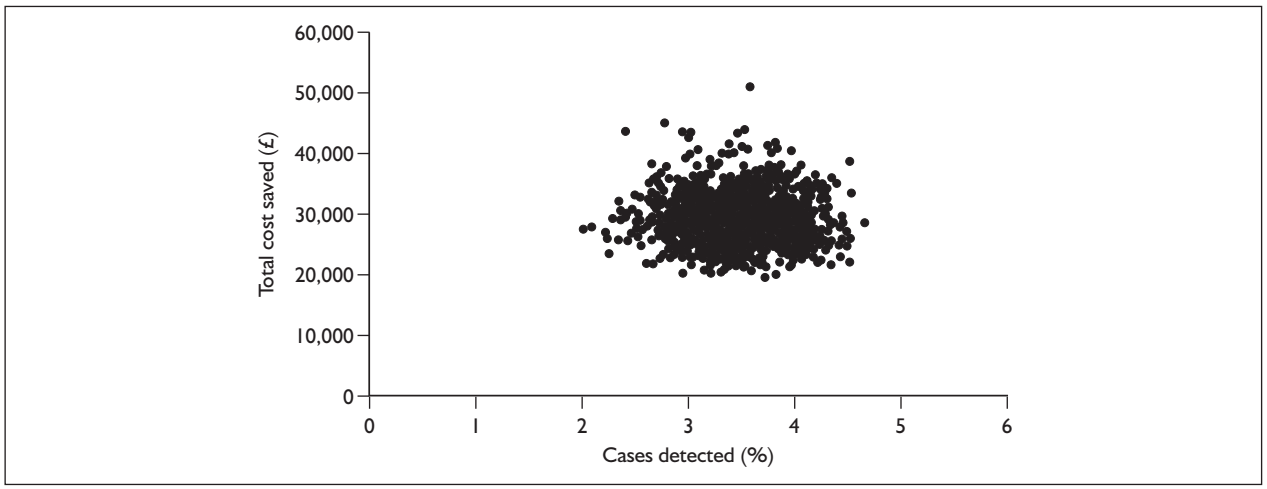

FIGURE 9 *Probabilistic sensitivity analysis results for cases detected and total costs saved for offspring family testing decision tree.*

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We look forward to hearing from you.

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ISSN 1366-5278