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EASL International Consensus Conference on Haemochromatosis

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Part I. Introduction

Iron overload diseases are frequent conditions associated with hereditary or secondary disturbances of iron metabolism. Hereditary haemochromatosis (HC), which is characterised by a genetic predisposition to absorb excess iron from the diet, is the most frequent form of genetic iron overload and one of the most common hereditary metabolic diseases in Caucasians.

Individuals with mutations in the recently-discovered haemochromatosis-associated *HFE* gene carry a risk of developing HC, a disease which can lead to liver cirrhosis, hepatocellular carcinoma, diabetes, cardiomyopathy, impotence and arthritis. Once diagnosed, the disease is efficiently treated by phlebotomy. Identification of the predisposition early in the course of the disease permits effective prevention. The fact that at the time of diagnosis many affected persons already have complications, such as diabetes, cirrhosis, or heart disease, indicates that better methods of early detection are needed. One approach to preventing iron overload disease is through enhanced case detection, by educating physicians about the early symptoms of iron overload, risk factors, diagnostic testing methods, and treatment. Another approach for early detection is through universal screening. In 1998, I was asked by the European Association for the Study of the Liver to organize the *EASL International Consensus Conference on Haemochromatosis*.

The objectives of the Conference were:

- To define the content to be used in educational materials for health care providers, patients and the general public on all aspects relevant to classification and nomenclature of human iron overload diseases and early detection, diagnosis and treatment of hereditary haemochromatosis from *experts.* Experts on haemochromatosis were individuals scientifically and professionally involved in haemochromatosis from the fields of internal medicine, hepatology, gastroenterology, haematology, genetics, bioethics, health service and management, and epidemiology.
- To ask a *jury*, on the basis of the evidence presented by the *experts*, to propose recommendations concerning early detection of hereditary haemochromatosis by evaluating the costs and benefits of different strategies from the point of view of society and from that of the individuals involved. The *jury* members included individuals not involved in haemochromatosis: methodologists, medical geneticists, genetic epidemiologists, internists, representatives of Haemochromatosis Associations, bioethicists, haematologists, clinical pharmacologists, hepatologists, social scientists, and clinical epidemiologists.

The consensus process involved different steps. First, from December 1998 through April 1999, the experts worked on a draft document and relevant literature citations. This document, representing the basis for the educational material (objective 1) and for the recommendations of the jury (objective 2), had to consider the following points:

Nomenclature and Classification of Haemochromatosis

Question 1: Prevalence

- What is the prevalence of different iron overload states due to HC along the continuum from asymptomatic accumulation of iron to life-threatening organ dysfunction?
- What is the appropriate terminology for different iron overload states along the continuum?
- Is it appropriate or feasible to define an over-accumulation state distinct from haemochromatosis?

* The views expressed in the jury document are not necessarily those of the WHO Secretariat.

Question 2: Genetics
- What proportion of HC is due to known *HFE* mutations?
- What proportion of HC is due to *HFE* mutations in different racial/ethnic groups?
- What is the penetrance of different *HFE* genotypes?
- What non-genetic factors influence penetrance of different *HFE* genotypes?

Natural History, Diagnostic and Therapeutic Aspects of Haemochromatosis

Question 1: Health impact
- What mortality and morbidity are attributable to HC?
- What proportion of liver disease, diabetes, arthritis and cardiomyopathy can be attributed to HC?
- What proportion of the morbidity and mortality caused by HC can be prevented by treatment?
- What proportion of people with asymptomatic HC progress to life-threatening complications if untreated?
- Do life-threatening complications of HC occur in asymptomatic persons?
- What are the best treatment strategies for HC?

Question 2: Treatment
- At what point should treatment be initiated?
- What are the early signs and symptoms of HC?
- Are all early signs and symptoms reversible?
- At what stage of HC do the signs and symptoms become irreversible?

Population Screening of Haemochromatosis

Question 1: Methods of early detection
- What is the predictive value of different methods of early detection (serum iron measures *vs*. *HFE* mutation tests)?
- Is predictive value affected by the presence or absence of symptoms?
- Is predictive value affected by the presence or absence of a biological relative with HC?
- Is predictive value increased by the use of both testing strategies, either concurrently or sequentially?

Question 2: Implications of early detection
- What benefits, costs and potential harms should be considered in evaluating different methods of early detection?
- What benefits to society should be considered (including prevented cases of disease, reduced health care costs, and, in some countries, increase in the blood donor pool); as well as costs and potential harms (e.g. the costs of screening and diagnostic tests, interventions and follow-up, associated investments such as physician and consumer education, laboratory quality control, and, in some countries, potential reduction in blood donor pool)?
- What benefits, costs and potential harms to individuals should be considered (e.g., benefits in terms of reduced morbidity and mortality, and reduced health care costs; costs, including time and medical costs associated with testing, follow-up and treatment; and potential harms including stigmatization, loss of health, disability or life insurance, anxiety or psychological distress)?

During the second step, the experts had the opportunity to meet and work on the draft document during the World Iron Conference BioIron '99 held in Sorrento, Italy, May 23–28, 1999. The co-ordinators of the three groups presented the content of the Expert Document to the consensus jury during a public session on Thursday, May 27, 1999.

The jury considered the evidence presented by the experts in written reports and public discussion. The presentation of evidence to the jury included the opportunity for additional public comment by meeting participants. After a period of review, from June 1999 to February 2000, the jury has released a final statement. In the Jury Document, the jury, on the basis of the evidence provided by the experts, was asked to answer the following main questions:

1. What is "haemochromatosis" and how should it be defined today?
2. What is the epidemiology and health impact of HC?
3. What is the clinical course of HC ?
4. What is the best diagnostic strategy?
5. What are the priorities for patients' and health care providers' education?
6. Is population screening warranted?
7. What are the ethical, social and policy issues in population screening for HC?
8. What are the research priorities?

In this issue of the *Journal*, the Expert Document and Jury Document are both published.

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Part II. Expert Document

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This document summarises the discussion and the conclusions reached by the three different expert groups[1] engaged in the consensus conference

1. Nomenclature and Classification

1A. *Prevalence*

The precise frequency of the different iron overload states due to haemochromatosis (HC) is unknown and need to be addressed in population studies (1,2). The appropriate terminology for different iron overload states along the continuum is given below. The expert panel considers it both appropriate and feasible to define an over-accumulation state distinct from haemochromatosis. "Excess body iron storage" (iron overload) [haemosiderosis=iron staining in tissues] may be: i) Minimal: ~1.5 g (hepatic iron concentration, HIC, >30 μM/g) (?pathological significance: e.g. porphyria cutanea tarda (PCT); ii) Modest: 2–5 g (HIC >100 μM/g; serum ferritin approx 500 μg/l) (seen in chronic liver disease, haemolytic disorders, PCT, etc.); iii) Severe: >5 g (HIC >200 μM/g; serum ferritin approx 750 μg/l).

Tissue injury (e.g. hepatic fibrosis) occurs at 5–10 g, especially if other factors are present (e.g. alcoholism) (3–5). In fact, iron overload may be caused by different conditions – see below.

1B. *Genetics*

The proportion of HC due to known *HFE* mutations varies in different parts of the world. In countries like Australia with a predominantly Northern European population the vast majority of HC is due to the *HFE* mutations (6–9). The proportion of HC due to *HFE* mutations in different racial/ethnic groups is defined well in the publication by Merryweather-Clarke et al. (8). The available data on the penetrance of different *HFE* genotypes indicate that the C282Y genotype (homozygous) is the most penetrant, leading to iron overload in 60% or more of individuals. Other *HFE* genotypes are less common causes of iron overload and the percentage seems to vary in different countries. The only significant one, however, seems to be the compound heterozygote (C282Y/H63D). Precise data on penetrance in different populations are not yet available and await the results of surveys currently being undertaken. The non-genetic factors that influence penetrance of different *HFE* genotypes are: physiological and pathological blood loss, dietary intake of iron, and alcohol intake.

1C. *Definition of HC*

After much deliberation the expert group reached the consensus on definition and classification given below, on the basis of the following. The term "haemochromatosis" was coined by von Recklinghausen in 1889 to describe the association of tissue injury (usually cirrhosis) with increased tissue iron. Other terms were suggested, e.g. bronze diabetes, and it was the English physician Sheldon (10), who, after conducting a comprehensive review of the literature to 1935, concluded that: "Haemochromatosis is despite its implicit and unproven assumptions the best name for the disease". Sheldon, in recommending the use of the term "haemochromatosis" clearly was referring to the genetic, inherited disorder of iron metabolism: "The view advanced as the most reasonable explanation of haemochromatosis is that it should be classed as an inborn error of metabolism, which has an overwhelming incidence in males, and

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TABLE 1

1. (Hereditary) haemochromatosis (synonymous with haemochromatosis)
• Haemochromatosis, *HFE*-related C282Y homozygosity C282Y/H63D compound heterozygosity Other mutations
• Haemochromatosis, non-*HFE* related Juvenile haemochromatosis Autosomal dominant haemochromatosis
2. Acquired iron overload
• Iron-loading anaemias
• Thalassaemia major
• Sideroblastic anaemia
• Chronic haemolytic anaemias
• Transfusional and parenteral iron overload
• Dietary iron overload
• Chronic liver disease
• Hepatitis C
• Alcoholic cirrhosis, especially when advanced
• Non-alcoholic steatohepatitis
• Porphyria cutanea tarda
• Dysmetabolic iron overload syndrome
• Post-portacaval shunting
3. Miscellaneous
• Iron overload in sub-Sahara Africa
• Neonatal iron overload
• Aceruloplasminaemia
• Congenital atransferrinaemia

which at times actually has a familial incidence. It concerns the inner metabolism of probably all the cells of the body .... and shows itself in two ways – by a disturbance of the metabolism of melanin .... and by the formation of an iron-containing pigment in nearly all the tissues." It is a reasonable assumption (but not proven) that both von Recklinghausen and Sheldon were describing cases of *HFE*-associated hereditary haemochromatosis because reference was made to familial cases, and causes of secondary iron overload such as thalassaemia were relatively uncommon in those countries (Germany and England). The expert group definition of HC is the following: haemochromatosis (or hereditary haemochromatosis) is an inherited disorder resulting from an inborn error of iron metabolism which leads to progressive iron loading of parenchymal cells in the liver, pancreas and heart. In its fully developed stage, organ structure and function are impaired. The common form of this disease is due to homozygosity for the C282Y mutation in the *HFE* gene. However, other hereditary forms not due to *HFE* mutations are recognised (see Table 1).

Individuals detected as homozygous for the C282Y mutation but without iron overload are best characterised as such, i.e. as carrying the genetic mutation which may lead to haemochromatosis but not yet having the disease. There are four stages of the disorder: the genetic predisposition but no other abnormality; iron overload (approximately 2–5 g) but without symptoms; iron overload with early symptoms (lethargy, arthralgia); and iron overload with organ damage, especially cirrhosis. A classification of iron overload disorders is given in Table 1.

2. Natural History, Diagnostic and Therapeutic Aspects

This section is mainly a summary devoted to emphasising the main data on Diagnosis and Treatment presented and agreed by the experts.

2.1. *Morbidity*

2.1.1. *Identification of symptoms and signs*

The following are the main signs of HC:

- General signs: weakness (60%)
- Rheumatological symptoms: arthralgia/arthritis (30–40%)
- Hepatic signs: i) Hepatomegaly/cirrhosis: 60% (11); 32% (12); 22% (13); 13% (14); ii) Hepatocellular carcinoma: 5%.
- Endocrine dysfunction: diabetes mellitus 10–30%; sexual dysfunctions 10–40%.
- Heart symptoms: arrhythmia (20–29% M *vs* F); cardiac failure (15–35% M *vs* F).

2.1.2. *Factors influencing morbidity*

- Ascertainment bias: When comparing probands and relatives, all symptoms, except weakness, have a lower prevalence among relatives.
- Confounding associated pathologies: Diabetes and rheumatological signs are frequent in the general population and can be, in haemochromatosis patients, over-interpreted as belonging to the phenotypic expression of haemochromatosis.
- Co-factors of morbidity: a) Intrinsic factors: i) Age and sex: the picture is usually less severe and frequent in women; fatigue and arthropathy predominate in women (15); no severe liver disease is usually observed under 35 years of age. ii) Genetic factors: they can modulate the penetrance of the HFE gene. b) Extrinsic factors: degree of iron intake, of iron losses; co-factors targeting the same organs as iron overload, for example, alcohol (liver, pancreas); obesity (liver); hepatitis virus B/C (HBV/HCV) liver.

2.1.3. *Uncertainties regarding morbidity*

- Abdominal pain: This symptom is frequent in some studies (i.e. 56% for ref. 11), whereas it is no longer mentioned in recent series.
- Infection. The prevalence of HBV and HCV has

been shown to be increased in patients with haemochromatosis. But, with regard to bacterial infection, besides reported cases of *Yersinia* infections, the largest series in the literature do not mention sepsis as being a significant problem in haemochromatosis.
- Atherosclerosis: Despite the reported high levels of transferrin saturation in cases of coronary heart disease, atherosclerosis has not been a reported finding in the various haemochromatosis series (11,16).

2.1.4. *Uncertainties regarding co-morbidity*
Initial studies (17) suggested a high incidence of extrahepatic cancers. But they were not confirmed by larger series (11,12,18,19). However, it remains possible that severe morbidity due to HC precluded the search for extrahepatic cancer, and that increased mortality rate related to major haemochromatotic complications masked the expression of extrahepatic cancers.

2.2. *Mortality*
2.2.1. *Frequency*
There is an increased risk of early death as compared to the normal population:

- Untreated patients: A classical (and unique) series (17) indicates poor survival rates 5 and 10 years after diagnosis (18 and 6%, respectively).
- Untreated and treated: Yang et al. (20) reported that haemochromatosis represented 0.017% of all deaths in US between 1979 and 1992; the age-adjusted mortality rate was 1.8 per million in 1992; the risk, higher in men, increased dramatically at 45 in men and 55 in women.
- Treated: Niederau et al. (11) reported that, for 251 patients studied between 1947 and 1991 (mean follow-up 15 years), cumulated survival was 93% at 5 years and 77% at 10 years, which was significantly reduced when compared with the expected survival rates for an age- and sex-matched normal population.

2.2.2. *Causes of mortality*
- Liver: The death rates compared with expected rates in the normal population were (11) 10 for liver cirrhosis, and 119 for hepatocellular carcinoma (HCC). Furthermore, the relative risk of HCC was 4.9-fold in HBsAg positive patients (21).
- Diabetes: mortality ratio=14.
- Cardiomyopathy: mortality ratio=14.

2.3. *Special issues relative to clinical expression of HC over the spontaneous course of the disease*
2.3.1. *Early signs* versus *delayed signs*
- Early bio-clinical symptoms: i) Weakness; ii) Arthralgias: Three main arguments: 1) as frequent in non-cirrhotic as in cirrhotic patients; 2) similar amount of mobilisable iron for patients with and without arthropathy; 3) increased prevalence (48%) in the period 1982–1991 as compared to the periods 1970–1981 and 1947–1969 (45 and 39%, respectively) despite a markedly increased rate of non-cirrhotic in the most recent period; iii) Increase of serum transferrin saturation.
- Delayed signs: i) Cirrhosis; ii) Diabetes mellitus; iii) Cardiac failure.

2.3.2. *Uncertainties regarding the early or delayed nature of some signs*
- Impotence: This can be considered as a rather delayed symptom if one takes into account: i) its decreased prevalence over the follow-up periods (57%, 31%, 20%, ref. 11), and ii) its lesser frequency in non-cirrhotic *versus* cirrhotic patients (27 *vs* 43%). However, the risk of underestimating this symptom is high, due to the fact that, often, patients do not spontaneously report this problem.
- Hepatomegaly: This could belong to early signs since it has been reported in 70% of non-cirrhotic patients.
- Skin pigmentation: This has been reported as delayed but was not different between non-cirrhotic and cirrhotic patients (69 *vs* 75%) (11); therefore, it might be more overlooked than delayed.
- Transaminase increase: This could be an early sign since it was reported in 49% of non-cirrhotic patients; however, according to George et al. (22), cytolysis could then be due to coexisting fatty liver.
- Methodological problems in assessing precocity or not of symptoms: the capacity to diagnose early signs depends on: i) clinical awareness, and ii) the performance of diagnostic tools. For instance, for cardiac symptoms it is possible to detect abnormalities before clinical signs of arryhthmias or cardiac failure if orientated echocardiography is performed (23).

2.3.3. *Asymptomatic* versus *life-threatening complications*
May clinically asymptomatic patients in fact present life-threatening complications? The answer is positive. Based on family studies (12), diabetes was found in 16% of patients and cirrhosis in 5% of male subjects detected by family screening.

Based on proband studies (11), 5% of cirrhotic patients were asymptomatic at the time of diagnosis.

2.3.4. *Asymptomatic* versus *non-life-threatening complications*

May clinically asymptomatic patients never present life threatening complications? The answer is yes:

- Systematic screenings, by detecting the absence of clinical expression of haemochromatosis in adults and especially in elderly subjects, provide increasing evidence that some C282Y +/+ subjects do not develop iron-related significant morbidity during their lifetime. Refer to the problem of penetrance of *HFE* genotypes (Section: Prevalence).
- However, this seems to occur in a low proportion of subjects: it is estimated that only 5% of C282Y+/+ men over the age of 40 years will not express an HC phenotype.
- Wider screening of subjects is needed to answer this question.

2.4. *Diagnostic strategy*

- *Can, in a given individual, the diagnosis of HC be ascertained using a non-invasive strategy, i.e. without a liver biopsy?*

Until the discovery of the *HFE* gene in 1996 by Feder et al. (6) the ascertainment of the diagnosis was, in most cases, based on liver biopsy, which: i) proved iron excess, ii) indicated its peculiar distribution, that is to say cellular (=mainly hepatocytic) and lobular (=decreasing gradient from the periportal to centro-lobular areas), and iii) allowed the determination of hepatic iron concentration and hepatic iron index (HII) (=ratio of hepatic iron concentration over age). An HII >1.9 strongly suggested, in the absence of other obvious causes of iron overload (especially transfusions), that the patient presented homozygote haemochromatosis.

Since the *HFE* discovery, two main diagnostic situations occur:

- *The patient, after clinical (=one or several of the previously described symptoms and signs) and/or biochemical (=increased transferrin saturation) suspicion of iron overload, is C282Y+/+*: Homozygosity is ascertained on this basis alone and does not need further confirmation. Then, a general work-up is started in order to evaluate: a) the degree of iron overload, and b) the possible visceral and/or metabolic consequences of the disease. For iron excess evaluation, two main explorations are valuable: the level of serum ferritin which provides a good correlation with the degree of iron excess (provided confounding factors liable to interfere with its level, such as inflammation, cytolysis, or a dysmetabolic iron overload syndrome, have been ruled out). The second investigation which enables an accurate appreciation of iron overload is, if available, hepatic MRI (magnetic resonance imaging). Having taken into account the level of ferritin (and, if feasible, MRI evaluation), two schematic situations are then possible: a) The first corresponds to moderate iron excess. Then, no liver biopsy is needed and, after a general work-up guided by clinical evaluation (potentially involving serum transaminase, electro/echo cardiogram, joint and bone x-rays, glucose studies, hormonal tests), venesection therapy can be started. b) The second situation corresponds to an important iron excess. Then liver biopsy is mandatory in order to assess the presence of cirrhosis (or severe fibrosis) and iron-free foci (considered as pre-neoplastic lesions (24)). If present, these lesions will lead to a specific follow-up for the detection of hepatocellular carcinoma. Therefore, in this new strategy, the major change is represented by the fact that *liver biopsy is no longer performed for diagnosis but for prognosis.* As to the criteria leading to the decision to perform a liver biopsy in C282Y+/+ patients, the study by Guyader et al. (25) has shown that in case of serum ferritin <1000 μg/l, *and* absence of hepatomegaly, *and* normal serum transaminase level (aspartate aminotransferase), it is not useful to perform a liver biopsy because there is no risk of significant liver fibrosis.
- *The patient, in whom pronounced iron overload is suspected by clinical and/or biochemical and/or imaging (MRI) data, is not C282Y+/+*. Liver biopsy is then often essential for diagnosis.

On the whole, since the prevalence of the genotypic C282Y +/+ profile is high among haemochromatosis subjects, in the large majority of cases liver biopsy is no longer needed for the diagnosis of haemochromatosis.

2.5. *Treatment*

2.5.1. *Tools*

- Venesection therapy is the key tool.
  It consists of 400–500-ml phlebotomies each week.
  It is conducted until ferritin <20–50 μg/l and transferrin saturation <30%.
  It is followed by maintenance venesections consisting of several phlebotomies a year.
- Strict iron-deficient diet is not recommended but iron-rich food should be avoided (red meat or liver). Iron supplements and vitamin C must be avoided. Tea drinking is beneficial.
- Chelation therapy by prolonged subcutaneous

desferrioxamine is almost never performed, and restricted to rare contra-indications to venesection therapy.

2.5.2. *Tolerance*

Tolerance is, on the whole, clinically and haematologically (Hb) good. However, it is not perfect. As shown by Moirand et al. (13), 64% of 353 venesected patients expressed some disagreement or problems: related to venous puncture in 43% (152/349); immediate fatigue in 63% (220/340); tedious treatment (28%); personally annoying (8%); professionally annoying (6%).

2.5.3. *Efficacy*

- On iron excess: Constant and excellent.
- On survival rate: Survival rate is normal, provided neither cirrhosis nor diabetes is present at the time of diagnosis. In the case of cirrhosis, the overall prognosis remains far better than with other types of cirrhosis. In three main studies (German, Canadian and Italian series), survival at 5 and 10 years was 92%–75%, 72%–62% and 75–47%, respectively. Moreover, in the German report by Niederau et al. (11), life expectancy of cirrhotic patients was 10–20 years longer than that reported for other forms of liver cirrhosis, in particular the alcoholic form.
- On symptoms and signs. The efficacy is:

Good: for fatigue (55%); skin pigmentation (68%); abdominal pain (68%); hypertransaminasaemia (73%).

Average: for arthralgia (30%); non-insulin-dependent diabetes or impaired glucose tolerance (40%); cardiac signs (34% for electrocardiographic symptoms); non-cirrhotic fibrosis: 42% (30/71). In cirrhosis, an interesting finding is the beneficial effect of iron removal on the evolution of portal hypertension in haemochromatotic patients (26): after a mean of 6±4 years of follow-up, varices were improved or completely reversed in 26% of the patients *versus* 5% in the control group. Bleeding from varices was observed in only one patient with haemochromatosis against five controls. Of 22 patients with haemochromatosis in whom portal hypertension was unmodified or worsened, 16 had coexistent hepatic viral infection, which further emphasises the interference of non-iron-related co-factors.

Poor: for impotence (19%).

Absent: i) for cirrhosis (which has not been convincingly reported as being reversible in haemochromatosis, in agreement with what is known for other types of cirrhosis); ii) for preventing the development of hepatocellular carcinoma when cirrhosis was present at the beginning of the treatment.

2.5.4. *Symptomatic treatment of visceral complications*

- Arthropathy: Non-steroidal anti-inflammatory compounds can offer significant help.
- Impotence: Androgens are usually efficient (but should be avoided in the case of fibrotic liver, because of the risk of facilitating the development of hepatocellular carcinoma).
- Liver: Alcohol ingestion should be discouraged (especially in the case of hepatic fibrosis); portal hypertension may benefit from classical symptomatic treatment; transplantation has only been performed in rare cases of well-documented haemochromatosis, with poorer results than in non-haemochromatotic indications.
- Diabetes: diet, oral compounds, and insulin can be applied as required.
- Heart: symptomatic compounds can be prescribed; heart transplantation has exceptionally been performed.

2.6. *Specific questions and uncertainties*

2.6.1. *Are there irreversible symptoms?*

The answer is positive for: i) Destructive arthritis, ii) Cirrhosis, and iii) Insulin-dependent diabetes.

2.6.2. *Are all early symptoms and signs reversible?*

The answer is negative: for instance, i) Weakness is unchanged in 40%, and ii) Arthralgia may not improve in 50% of cases.

2.6.3. *May some signs or symptoms worsen under therapy?*

The answer is yes: for instance, arthralgia may worsen in 20% of cases.

2.6.4. *May some signs or symptoms appear under therapy?*

The answer is positive: Despite treatment, fatigue, arthralgia and impotence may still develop, affecting 14% of patients for each feature (11).

However, in this series, patients were not totally asymptomatic and therefore this does not provide a real answer to the question of the fate of totally asymptomatic individuals discovered either through family studies or after systematic biochemical screening.

2.6.5. *What schedule of depletive strategy should be used in slightly overloaded patients?*

No documented answer; however, there is probably no need to use the 400–500-ml weekly regimen, which should be confined to important iron excess.

2.6.6. *At what age should venesections be started in young, clinically asymptomatic individuals?*
There is no definite answer, only some clues:

- Iron needs are important during infancy and adolescence.
- No cirrhosis and/or complications of chronic liver disease were seen, in two recent reports, under the age of 35 (unless there was a co-morbid insult such as alcohol or virus). Therefore, it is reasonable to assume that, in general, if diagnosis and treatment are initiated prior to age 35 all major hepatic morbidity from the disease can be prevented. However, it should be noticed that in Niederau's series the youngest cirrhotic patient was 24 and in the historical description by Trousseau (27) the patient was 28.
- In two large series of symptomatic patients, the youngest subjects were 18 and 19 years old. Based on these data, it seems wise to propose venesection therapy from 18 years of age.

3. Population Screening

The following principles were agreed upon by the Expert Committee:

The Expert Committee strongly supports ongoing and planned studies on population screening for haemochromatosis

The committee reviewed a body of data from studies in which the initial screening test was either iron status markers (transferrin saturation, unbound iron binding capacity, ferritin) or *HFE* mutation analysis (C282Y and H63D mutations). Screening studies have been carried out or are under way in over 15 countries and a large-scale screening project of 100 000 Americans is planned. These studies emphasise the interest in the subject. Some committee members felt that the presently available evidence was sufficient to recommend population screening. Others concluded that given the uncertainties about disease penetrance (the proportion of affected individuals who will develop serious clinical expression of disease) and the risk for clinical manifestations that can be specifically attributed to haemochromatosis, it was premature to recommend screening. It is anticipated that in the future, grant-funded research projects may progress to population-based demonstration projects in which initial screening test costs are reimbursable by third-party payers.

The current rate of late diagnosis of haemochromatosis is unacceptable

Haemochromatosis is most commonly found incidentally (12). Diagnostic testing in patients with symptoms of haemochromatosis is appropriate clinical practice and many of these patients improve with venesection therapy. However, the diagnosis within groups with potential symptoms of haemochromatosis, such as liver disease, diabetes, arthritis, impotence and fatigue, has not been highly effective in preventing morbidity since irreversible organ dysfunction is often present (1,11,15). More recent studies have shown a lower percentage of affected individuals with life-threatening complications at diagnosis (11,12,28). It is not clear whether this is an effect of screening or of enhanced case detection due to greater clinician awareness about haemochromatosis and a higher index of suspicion in patients with early non-specific symptoms. Future efforts to improve the rate of early diagnosis will include educating physicians and patients about haemochromatosis (29), as well as research projects involving screening in populations at risk for this disease.

Genetic testing for the C282Y mutation of the HFE *gene offers a new population screening strategy in Caucasian populations of European heritage*

The recognition that more than 90% of clinically diagnosed haemochromatosis patients of Northern European heritage are homozygotes for the C282Y mutation of the *HFE* gene, has provided a new screening test for haemochromatosis. Screening strategies using phenotypic testing (transferrin saturation, ferritin) have been effective at identifying iron-loaded individuals in the general population (30–34). However, the protocol for identifying the cause of the iron overload has generally involved a complex sequential visit and testing algorithm that often includes liver biopsy (25). Furthermore, the sensitivity and specificity of screening tests such as transferrin saturation have been based on a case definition of iron overload (haemochromatosis=iron overload). If you define haemochromatosis by the presence of an elevated transferrin saturation and ferritin the sensitivity is high (self-fulfilling strategy). The recognition that more than 90% of clinically diagnosed haemochromatosis patients of European heritage are homozygotes for the C282Y mutation of the *HFE* gene, has provided a new diagnostic test that obviates the need for liver biopsy in most cases. Genotyping has also led to the recognition that not all C282Y homozygotes progress to significant iron overload and clinical manifestations, and some C282Y homozygotes do not have iron overload (incomplete penetrance) (35,36). There is no universal agreement within the panel about whether these non-expressing homozygotes should be considered to have haemochromatosis. However, the identification of these non-expressing homozygotes has led to the discovery of

iron-loaded family members (37). Iron overload indistinguishable from hereditary haemochromatosis has been found in patients who are neither homozygous nor heterozygous for the C282Y mutation (e.g. wild-type or H63D homozygotes). Some panel members characterise these patients as having hereditary haemochromatosis, while others consider them to have an iron overload disorder of a different (and currently unknown aetiology). In these cases, C282Y testing is not a useful screening test.

Different strategies are likely to be optimal in different countries

In some countries, such as Italy, many iron-loaded patients are not homozygotes for the C282Y mutation, and the prevalence of this mutation is lower in the general population (38). Therefore, phenotypic screening would seem preferable in countries with a low prevalence of the C282Y mutation. C282Y genotyping is most useful in countries with a high prevalence of haemochromatosis related to this mutation. This includes Northern Europe and Portugal and countries dominated by immigration from Europe (Australia, Canada, United States) (39). For example, in Ireland, where the prevalence of haemochromatosis may be as high as 1 in 100, and more than 95% of typical cases are C282Y homozygotes, genotypic screening may be the preferred strategy (40). Iron overload has also been described in Africans and African-Americans (41,42). African-American populations vary widely with respect to their African area of origin and their degree of Caucasian and non-Caucasian genetic admixture. The extent to which the interaction of presumed African-American iron overload genes, inheritance of *HFE* mutations, and other genetic and environmental factors may cause iron overload requires further study.

Economic impact of screening strategies

Two strategies are commonly proposed. Phenotypic screening (transferrin saturation) followed by C282Y testing to identify homozygotes or genotypic screening (C282Y genotyping) with subsequent testing for iron overload with transferrin saturation and/or ferritin. Economic analysis has demonstrated that from a third-party payer perspective either strategy could be cost effective (43,44). Societal costs (anxiety, unnecessary treatment, genetic discrimination) and indirect costs have often not been included in decision analysis models, but this applies to most cost evaluations in other diseases. The cost and/or benefit of detecting patients with alcoholic liver disease, chronic viral hepatitis and iron-loading anaemias by phenotypic screening has not been included in these analyses. The existing cost studies make screening appear cost-effective using the same criteria applied to other health maintenance measures, such as cholesterol screening. Randomised trials comparing screened and non-screened populations with long-term follow up will be unlikely because of ethical concerns about potentially preventable morbidity and mortality in the non-screened population. The majority of the committee supported the strategy of phenotypic testing in young adults followed by genetic testing (45). This strategy is designed to detect C282Y homozygotes that may require venesection therapy. A comparison of these two screening strategies is shown in Table 2.

Further information on penetrance of disease will be forthcoming in screening studies already in progress

The major concern expressed with regard to the implementation of population screening is the lack of conclusive data about penetrance of the gene. This can be defined in several ways: 1) the percentage of individuals with an elevated transferrin saturation and/or ferritin; 2) the percentage of individuals who develop symptoms of haemochromatosis; and 3) the percentage of individuals who develop life-threatening symptoms of haemochromatosis (cirrhosis, hepatocellular carcinoma, diabetes, heart failure). One pedigree study has

TABLE 2

Screening strategies

Initial screen – phenotype (Transferrin saturation)

- Strengths
  - Used successfully in many population-based screening trials
  - Testing readily available and relatively inexpensive
  - Reasonable estimates of sensitivity and specificity as a marker for iron overload
  - May detect iron deficiency
- Weaknesses
  - Larger number of individuals require follow-up (1–6% or more depending on cut-off level chosen)
  - Complex, multi-step process necessary to determine whether iron overload present and, if so, the cause of iron overload
  - Some uncertainty of disease progression

Initial screen – genotype (C282Y/C282Y only)

- Strengths
  - Simple testing strategy
  - Good estimates of genotype frequency available
  - Small number of individuals identified as "Screen Positive" (0.5% or less)
- Weaknesses
  - Genotype accounts for a lower proportion of cases in some areas
  - Uncertainty of disease progression
  - Higher cost of test
  - Issues surrounding identification of C282Y heterozygotes
  - Potential increased psychosocial risks associated with DNA-based testing

suggested that 43% of men and 28% of women will develop life-threatening complications (46). This is discordant with autopsy studies (20), but is likely related to an ascertainment bias and underdiagnosis. Preliminary estimates from screening studies have demonstrated that 19–58% of C282Y homozygotes will have iron overload as assessed by serum ferritin (37,47). It is important in a non-expressing homozygote to exclude pathological blood loss, regular voluntary blood donation or a false positive genetic test which can occur with a common 5569A polymorphism of *HFE* (48,49). Screening studies that include elderly individuals will help to answer the question of penetrance in the general population. A sample of 600 patients over age 70 demonstrated a prevalence of 1 in 150 for C282Y homozygotes, which suggests that homozygotes are not under-represented in an elderly population because of death from life-threatening complications (50). The question about the proportion of affected individuals who will progress from biochemical evidence of iron overload to serious clinical manifestations is the key to the decision about implementating population screening (51).

The benefits of early diagnosis and treatment will likely outweigh the potential risks of labelling, anxiety and genetic discrimination

The risk in life or disability insurance should be based on organ dysfunction rather than genetic status. Educational targets should include the insurance industry. Health insurance discrimination is another potential problem, and legislation is evolving to prevent discrimination. Physicians, patients and insurers must be aware of the excellent prognosis in patients diagnosed at an early stage of haemochromatosis.

The ideal population to screen is young Caucasian adults (about 30 years of age). Inclusion of individuals from other racial and ethnic populations with a known low prevalence of haemochromatosis is likely to decrease screening efficiency and increase cost per case detected

The age to begin screening has previously been based on the fact that transferrin saturation becomes elevated in the majority of individuals with hereditary haemochromatosis by this age. It has been suggested that genetic testing could be done at birth as part of newborn screening. Genetic screening of newborns has both ethical (limited consent) and logistic concerns (long-term follow up). The severity of these concerns varies between different countries. Organ damage due to haemochromatosis has been uncommon under the age of 40 (25). If a decision is made to implement population screening, it will be necessary to develop an effective method to obtain a sample from the young adult population who may not routinely be seen by health care systems.

Implementation of screening into routine clinical practice will require an intensive campaign of physician and patient education

The benefit of the current population screening projects will be to increase awareness of the prevalence of the condition and the appropriate diagnostic tests. Optimal communication strategies aimed at the patient include the internet, television, popular magazines and newspaper commentaries. Medical experts should play a greater role in verification of information provided on the internet about haemochromatosis since available information is not always accurate. It is possible that an extensive education campaign (practice guidelines, newsletters) may lead to appropriate early detection and treatment in primary care, which may alleviate the need for population screening.

The studies in progress may resolve current gaps in knowledge and lead to recommendation of population screening for haemochromatosis

Current and future studies will provide further information about key issues such as penetrance of *HFE* genotypes, disease progression, attributable risk, and the psychosocial impact of genetic testing. Future dialogue on population screening should include not only investigators, but representation from public health (52), genetics, insurance and health care organisations and patient groups.

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Part III. Jury Document*

Preamble

This document summarises the conclusions of a Consensus Panel (hereafter called "the Panel") convened by the European Association for the Study of the Liver in the framework of an International Meeting on Haemochromatosis held in Sorrento (Italy) on May 23–29, 1999. This panel was assembled as an independent group of experts from various disciplines, including: genetics, epidemiology, health services research, health educators, clinical pharmacologists, clinicians and a patient advocate.

These introductory paragraphs are provided to inform readers about the process used by the Panel to make its recommendations about haemochromatosis. The Panel members agreed that the process we used to arrive at clinical recommendations should be explicit and publicly accountable, so that users can judge the validity of the methods for themselves.

The Panel recognised that a range of processes is currently in use for making consensus recommendations. An example of an informal process might be to convene a group of experts to make recommendations based on their own experience, with the entire process taking an hour or less. An example of an extremely formal process is the emerging international standard for making evidence-based recommendations using a highly structured method with analytical frameworks, key questions, literature search strategies, inclusion and exclusion criteria, judgments of the quality of evidence, and formal linkages between the evidence and recommendations. Such a formal process might take many months to complete and be costly.

The process used by the Panel for the haemochromatosis exercise employed both formal and informal methods. Groups of experts (hereafter called the Expert Group) were first convened over several months to write review papers, citing evidence in three general areas. These papers were presented to the Panel at the conference. The Panel began its deliberations by reformulating the key questions proposed in the review papers. After general discussion, small groups of Panel members worked on summaries and recommendations, and then presented proposals to the entire group for further discussion and refinement.

The Panel judged that the Expert Group review documents cited most of the known evidence on the topics of interest. However, evidence from the individual studies was not critically appraised and, according to content experts on the Panel, there was no acknowledgement that some of the studies were seriously deficient in their methods. Members of the Panel also pointed out major gaps in the reviews, especially in the balance of benefits and harms, and in ethical and public policy perspectives.

In consequence, the Panel elected to take a fundamentally conservative approach by making a limited number of statements and recommendations on issues that could be addressed with confidence, even against the backdrop of an evidence base of varying and, in some cases, unknown quality.

On the key question of recommending for or against population-wide screening for haemochromatosis, the Panel was especially conservative, finding that the standard of evidence for making a positive recommendation has not yet been met.

1. What is Haemochromatosis?

1.1. *General definition*

Haemochromatosis (HC) is a condition in which iron loading of the liver, pancreas, heart, and other organs impairs the function and damages the structure of

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* *Members of the Panel:* Alessandro Liberati (Chairperson, methodologist), Jean P. Benhamou (Hepatologist), Albert Berg (Methodologist), Suzanne Braga (Medical geneticist), Dorit Carmelli (Genetic epidemiologist), Timothy Cox (Internist), Janet Fernau (Haemochromatosis Association), Norman Fost (Bioethicist), Lucio Luzzatto (Haematologist-Geneticist), Nicola Magrini (Clinical pharmacologist), Michael Manns (Hepatologist), Nancy Press (Social scientist), William Rosenberg (Clinical epidemiologist and hepatologist), Juan Rodés (Hepatologist), Gilbert H. Welch (Health policy and Screening). *Writing Committee*: Albert Berg, Timothy Cox, Norman Fost, Alessandro Liberati, Lucio Luzzatto, Nancy Press and William Rosemberg.

these organs[1]. Hereditary HC – synonymous with primary iron overload or primary HC – is a disorder due to inappropriately increased iron absorption in which iron loading of parenchymal cells in the liver, pancreas, heart and other organs impairs the function and damages the structure of these organs. This condition is caused by inborn errors of iron metabolism. While the presence of mutations in the haemochromatosis gene (see below) indicates the existence of the genetic form of HC, the clinical diagnosis of hereditary HC is made when iron overload is present. A distinction should be made between hereditary HC and HC that indirectly results from other conditions that bring about iron overload (secondary HC).

1.2. *Classification*

A. *Hereditary haemochromatosis:*

1. HFE related (1).
   C282Y homozygosity.
   C282Y/H63D compound heterozygosity.
   Other mutations.
2. Haemochromatosis – non-HFE related.
   Adult form (2).
   Juvenile form[2] (3).
3. Autosomal dominant haemochromatosis.
   A single large pedigree has been reported from the Solomon Islands.

B. *Secondary haemochromatosis:*

1. Anaemias associated with ineffective erythropoiesis (e.g. thalassaemia intermedia, sideroblastic anaemias).
2. Other haemolytic anaemias[3].
3. Repeated red cells transfusions (e.g. for the management of aplastic anaemia).
4. Chronic liver diseases[4].
5. Excessive iron ingestion (especially in those foods or drinks from which it is more readily absorbed).
6. Dysmetabolic iron overload syndrome
7. Acaeruloplasminaemia
8. Atransferrinaemia
9. Neonatal (or perinatal) iron overload.

[1] The term HC simply describes accumulation of excess iron in tissues.

[2] In several families linkage to chromosome 1q21 has been established.

[3] In these conditions iron overload is likely to be more severe when the patient harbours a mutant HFE allele.

[4] In various forms of hepatic disease (e.g. alcoholic liver disease, cirrhosis, hepatitis C, non-alcoholic steatohepatitis, porphyria cutanea tarda, Wilson disease after penicillamine treatment) iron accumulates principally in the liver; thus, this form of iron overload may not fulfil the stated definition of HC.

2. What is the Epidemiology and Health Impact of Hereditary HC?

2.1. *Epidemiology*

According to a recent review of epidemiologic data carried out by the French Agency for Accreditation and Technology Assessment (ANAES) the worldwide prevalence of hereditary HC in people aged 18–70 is between 1.5 and 3 per thousand. In more recent studies these values have been somewhat higher, ranging between 1.6 and 5.9 per thousand. The male/female ratio is 2.2 to 1; women may develop symptoms at a later age and in a milder form, probably due to repeated blood losses from menstruation and pregnancies. Between 10% and 13% of individuals of Northern European heritage are carriers of hereditary HC.

2.2. *The health impact of haemochromatosis*

Many studies have helped to outline the clinical features of hereditary HC. However, the methodologies employed do not allow accurate estimates of the morbidity and mortality attributable to hereditary HC. Studies of the clinical course are often confounded by ascertainment bias: case series collected in referral centres overestimate case severity (4); studies of blood donors (which exclude persons with clinical or laboratory abnormalities) underestimate case severity (5). Studies carried out on persons belonging to high-risk families (e.g. kinship studies) may also be misleading. Because the effect of co-existing modifier genes and shared environmental exposures cannot be independently assessed, the penetrance of the homozygous state is likely to be overestimated (6).

Previous studies have estimated the prevalence of iron overload or the frequency of genotypes associated with hereditary HC. Values of between 1 and 10 per 1000 have been obtained in populations of European origin for both the prevalence of iron overload (7) and the prevalence of the homozygous state for C282Y (8). However, these data do not prove that these persons have hereditary HC. In fact, there is a wide gap between both the frequency of iron overload and the frequency of homozygous C282Y (see Genetics), both of which are 1–10 per 1000, and the frequency with which hereditary HC is diagnosed (about 1 in 10 000).

3. What is the Clinical Course of Hereditary HC?

There are no inception cohort studies that can determine the course of hereditary HC in any population. The best available information was cited in the Expert Group's review document and is derived from the account of the long-term case series from Düsseldorf reported by Niederau and colleagues (4). This cohort of

251 patients was compared with age- and sex-matched control subjects but contained a high proportion of patients with cirrhosis and diabetes. Life expectancy in those patients who were free of cirrhosis at the institution of venesection therapy was indistinguishable from that in the control group. In comparison with historical controls, even cirrhotic patients derived a survival advantage from venesection. Hepatocellular cancer was the most common cause of death (9).

Additional information was derived from the earlier case series in London (UK) reported by Bomford & Williams in 1976 which provided evidence that, compared with historical control patients with untreated hereditary HC, iron depletion by venesection improved outcome and survival, even in those patients with established cirrhosis. In this retrospective study, an estimate of the natural course of hereditary HC in the absence of venesection treatment was provided: the percentage survival 5 and 10 years after diagnosis was 18% and 6%, respectively (10). Deaths occurred principally from the complications of cirrhosis and diabetes mellitus, as reported in the earliest literature.

Two further studies suggest that early diagnosis of patients identified either by screening family members of affected individuals (11) or by screening laboratory test results (5) reduces the incidence of disease manifestations, including cirrhosis, during subsequent follow up.

As stated by the Panel, these latter studies, which have limited follow-up and mortality data, cannot definitively determine the long-term relationship between iron depletion and outcome. In addition, all these studies are subject to different ascertainment biases, each of which would operate to exaggerate the benefit of venesection treatment. Further, no evidence was presented to determine the relationship between *HFE* genotype and response to venesection treatment. However, in the light of the universally favourable outcomes reported hitherto, we must recognise that randomised controlled trials of venesection are no longer ethically justifiable.

Since the identification of a genotype that has been shown to confer susceptibility to hereditary HC, it will now be possible to determine the course of iron loading and the evolution of its clinical manifestations. Whilst the expert panel cited some studies that have attempted to investigate the age-related morbidity of individuals harbouring mutations in the *HFE* gene, as stated earlier no definitive information has yet emerged from inception cohort studies. Early data have emerged from at least one population-based cohort study (the Busselton Study) (12) and long-term follow-up should be highly informative, although the number of homozygous subjects identified is small.

Research groups in St. Louis (13) and Rennes (14) have not observed cirrhosis in patients under the age of 40 years in the absence of hepatitis C or excess alcohol ingestion, and have thus suggested that major morbidity from the disease can be prevented if treatment is initiated before this age. The ascertainment bias that inevitably confounds such studies unfortunately reduces their ability to predict outcome in this way.

The Panel recognises the critical need to answer these questions, which will provide the information necessary for a comprehensive and accurate description of the course of hereditary HC in different populations. This information will be required for the design of improved public health policies for the investigation and management of hereditary HC, and in particular the development of screening programmes. Furthermore, definitive information about the evolution and outcome of hereditary HC would enhance the quality of physician and patient education programmes. While such information would conventionally be obtained from inception cohort studies, it was recognised that the very long evolution of hereditary HC precludes the acquisition of these data in a reasonable time. An alternative method, such as cross-sectional sampling, might be used instead.

Thus, much is already known about the clinical picture and laboratory test results of hereditary HC diagnosed through recognition of the clinical syndrome, through the investigation of the relatives of probands, and through screening some selected populations, including asymptomatic blood donors and asymptomatic company employees. These and other studies have described a range of symptoms, signs and laboratory test results that are said to be characteristic of hereditary HC. However, little is known about the course of hereditary HC in patients diagnosed through mass screening programmes in unselected populations, and little is known about the outcome of venesection

TABLE 1

Serum tests in iron overload

Test	Levels in iron overload	Normal range
Transferrin saturation (1)	>45%	M=20–40% W=15–25%
Unbound iron binding capacity (2)	<28 μMol/l	
Ferritin (3)	M>300 μg/l W>200 μg/l	

(1) See diagnostic strategy.
(2) Equivocal test results on random samples may require repeated testing of fasting samples.
(3) Ferritin is an acute phase protein and so may be raised in a range of inflammatory conditions and tumours. This must be considered when interpreting test results.

treatment of patients identified through such programmes. Although this will encompass, and is likely to be similar to that already described, this information is essential if the full cost and benefit of mass screening programmes in different populations are to be determined.

4. What is the Best Diagnostic Strategy?

The Panel considered papers presented by the Expert Group and additional information concerning diagnostic tests in the investigation of the individual diagnosis of hereditary HC.

4.1. *Diagnostic tests*

4.1.1. *Serum tests of iron overload*: When hereditary HC is suspected, three serum tests are used to identify individuals with iron overload: transferrin saturation (TS), unbound iron binding capacity (UIBC) and ferritin (Table 1). The levels presented in the Table as being indicative of iron overload have been determined in selected populations, mainly healthy blood donors, with clinically diagnosed hereditary HC as the gold standard. These levels may not be appropriate in other populations and will need to be re-evaluated in the context of mass screening. Classically these tests have been performed on fasting blood samples. The Expert Group expressed the view that this was unnecessary if they are to be employed in the identification of hereditary HC cases, provided an appropriate cut-off level is used (e.g. 45% for TS) and equivocal samples are investigated further. Ferritin measurement is a highly sensitive test for iron overload and so normal levels essentially rule out iron overload. However, ferritin is not a very specific test because ferritin is an "acute phase protein" and thus elevated values can be the result of a range of inflammatory conditions.

4.1.2. *Genetic tests:* Currently there are two identifiable molecular abnormalities associated with hereditary HC: homozygosity for C282Y mutation and compound heterozygosity for C282Y/H63D mutations. Studies addressing the phenotypic penetrance of H63D homozygotes are in progress. Other mutations are likely to be discovered in the future and will be followed by the development of additional serum tests to identify them.

The Panel emphasised that the disease hereditary HC is defined in terms of phenotype, not genotype. Thus the identification of any one of the above mutations is, by itself, insufficient for the diagnosis of hereditary HC. Instead, the identification of the genetic abnormality provides evidence of susceptibility to developing the phenotype. The panel recognises that non *HFE*-genes are also likely to play a role in hereditary HC, both in directly conferring susceptibility and as modifiers of *HFE* mutations.

The prevalence of C282Y and H63D mutations has been reported in case-series of patients with hereditary HC, targeted groups of individuals with clinical disorders associated with hereditary HC (15–19) and selected populations, including healthy blood donors (8). No report of the prevalence of these mutations in unselected populations was submitted to the Panel.

4.1.3. *Provocative testing: quantitative venesection:* An alternative method for assessing the extent of iron overload is by measuring the total number of phlebotomies required to obtain a normal serum iron and ferritin. If a substantial amount of iron can be removed by venesection without inducing iron deficiency anaemia, physicians can be confident that iron overload was present. As shown in Table 2, what constitutes a substantial amount of iron (and thus the number of units) differs in men and women.

4.1.4. *Liver biopsy*: Traditionally, the gold standard for diagnosing hereditary HC has been the quantitation of hepatic iron and observing the histological distribution. Obviously, this gold standard entails a liver biopsy – with the attendent morbidity and mortality risks. The Panel recognised that the emergence of biochemical and genetic testing may allow the avoidance of liver biopsy in the vast majority of cases. However, in equivocal cases of hepatic iron overload histological examination of the extent and distribution of iron loading are required to diagnose hereditary HC. The Panel also recognised that the routine use of liver histology could adversely affect the net benefit of any broad-based effort to diagnose the disease early.

TABLE 2

Amount of iron to be removed by venesection according to sex

	Males	Females
Iron to be removed (g)	5	3
Number of units (assuming 225 mg/unit)	22	13

TABLE 3

Classification for staging iron overload

	Hepatic iron concentration (μmol/g dry weight)	Associated total body iron store	Associated serum ferritin
Minimal	>30	~1.5 g	male <300 μg/l; female <200 μg/l
Moderate	>100	~2–5 g	~500 μg/l
Severe	>200	>5 g	~750 μg/l

Hepatic iron may be quantified either by semi-quantitative staining or by measurement of dry weight liver iron (Hepatic Iron Concentration, HIC). Table 3 shows the classification for staging iron overload defined by the Panel. The Hepatic Iron Index (HII) (dry weight liver iron concentration/age) is one method for differentiating hereditary HC from other iron overload states (particularly that associated with alcohol abuse). An HII >1.9 is indicative of hereditary HC[5].

Histological distribution of iron: the presence of iron in hepatocytes with a decreasing gradient from periportal zone to centrilobular area is typical of but not specific for hereditary HC. Relative sparing of Kupffer cells is typical of hereditary HC but is not seen in association with causes of secondary iron overload.

Raised transferrin saturation and decreased UIBC provide early information of iron overload. Ferritin and liver biopsy provide evidence of iron accumulation in tissues and tissue damage. Hereditary HC may be diagnosed in the presence of HII >1.9 or on the basis of the histological pattern of iron distribution in the liver; or quantitative venesection if liver biopsy is not feasible (20). Hereditary HC is highly unlikely if the TS is normal, the ferritin is normal and the genotype wt/wt.

4.2. *Diagnostic strategies*

In the previous section we have described diagnostic tests used in the investigation of iron overload syndromes. The detection of a genotype such as C282Y/C282Y or C282Y/H63D identifies a high risk for iron accumulation but is not tantamount to hereditary HC (see Definition above).

Excluding the diagnosis of hereditary HC: The need for increased awareness of hereditary HC by primary care providers is recognised by the Panel (see section 5 below). Because of the protean manifestations of hereditary HC and the likelihood of underdiagnosis, there is an important need to exclude hereditary HC as the cause of symptoms. It is suggested that the measurement of TS should be considered in the (otherwise unexplained) conditions reported in Table 4, and further investigations to exclude a diagnosis of hereditary HC should be performed in patients with TS >45%, to avoid missing the diagnosis and to facilitate instituting treatment for patients early in the course of disease[6].

Confirming the diagnosis of hereditary HC: Criteria essential for diagnosis of hereditary HC: evidence of iron overload and impairment of liver function or damage to liver structure. Criteria sufficient for diagnosis of hereditary HC: in the absence of a liver biopsy, quantitative venesection may suffice. Hereditary HC cannot be diagnosed or excluded solely on the basis of a genetic test result. In patients identified as C282Y homozygotes, further testing should be undertaken to exclude iron overload.

5. What are the Priorities for the Education of Patients and Health Care Providers?

The Panel agreed that underdiagnosis of hereditary HC is a problem that should be addressed through the education of physicians in primary care practice. The Panel also agreed that a significant barrier to conveying this message effectively was that physicians believe that they rarely encounter cases of hereditary HC in their practices. Therefore, it is suggested that a message be crafted which will persuade primary care physicians of the advantage of maintaining a high index of suspicion with regard to the possibility of a diagnosis of hereditary HC.

The suggested elements of such a message include:

- The reasoning behind the belief that hereditary HC is largely underdiagnosed.
- The possible contribution of hereditary HC to serious and common chronic conditions.
- The ease and effectiveness of treatment for hereditary HC, as well as the potential dangers when not treated.
- The simplicity of using a measurement of biochemical iron such as TS (see above).

The anomaly with regard to hereditary HC is the discrepancy between the prevalence of the genotype and the number of cases found either by clinical observation or from death records. While both sources of

TABLE 4

Conditions where a biochemical test to exclude hereditary HC should be considered

- Chronic parenchymal liver diseases including hepatocellular carcinoma
- Cardiomyopathy and arrhythmias
- Diabetes mellitus type I and II
- Impotence and loss of libido
- Amenorrhoea
- Infertility
- Anterior pituitary failure
- Arthritis and arthralgia (particularly in association with chondrocalcinosis)
- Inappropriate increased skin pigmentation
- Porphyria cutanea tarda

[5] Sensitivity 79–93%; Specificity 93–100%; Diagnostic efficacy 91–99% relative to clinical diagnosis of cases.

[6] Acknowledging that the impact of this strategy is presently unknown. The panel recommends that these issues should be addressed in future research.

case finding are subject to significant bias, the Panel finds it implausible that bias explains all of the discrepancy. This presents the possibility that the *HFE* gene may require the interaction of other genes and/or environmental factors to produce life-threatening conditions. However, it is also very possible that the genotype contributes to the risk of developing many chronic diseases (e.g. diabetes/heart diseases/arthritis and arthralgias, impotence and infertility), perhaps producing cases of these conditions that are, for example, more serious and/or of earlier onset. For this reason, and because treatment of underlying hereditary HC may ameliorate some of those other conditions, it is important and worthwhile for physicians to be alert to the possibility of hereditary HC as a contributor to these conditions.

In the vast majority of cases hereditary HC can be ruled out easily through the use of a test of transferrin saturation. As an initial screen a non-fasting sample can be taken, with a TS>45% considered indicative of a need for further investigation.

It is suggested that ruling out hereditary HC through the measurement of TS should be considered in the conditions listed in Table 4.

Caution must be exercised in relying on TS to exclude hereditary HC if there is any reason to suspect recent blood loss that might cause a temporary normalisation of TS.

5.1. *What are the implications of the hereditary HC gene for primary care practice?*

The discovery of the *HFE* gene and the characterisation of mutations associated with hereditary HC are an important step in understanding the nature of hereditary HC. The Panel in fact believes that *HFE* testing is an important addition to biochemical tests of iron status in the targeted investigation of patients with iron overload. On the other hand, the majority of the Panel believes that *HFE* testing has little role in screening, as opposed to targeted testing in primary care for the following reasons: (a) there are cases of hereditary HC where there is no mutation; this is especially likely to be the case in non-Northern European populations; (b) there are cases of a known mutation where there is no iron overload; (c) there are still gaps in knowledge about the natural history of the disease; and (d) there is a wide range of variation in the expression of symptoms in individuals with disease. The diagnosis of hereditary HC, therefore, must be based on phenotype rather then genotype.

However, once an individual has been diagnosed with hereditary HC – especially if there are family members who might also be at risk – a genetic test may help to characterise the risk of others in the family. If the individual were found to be homozygous for the C282Y mutation, then others in the family could be tested informatively. This could also eliminate the need for close surveillance in the 75% statistical chance of the individual not carrying the mutation.

It is important to remember that since this is an autosomal recessive disorder, the risk is greater to probands' siblings than to their children. This can be a difficult point for patients to understand, since concern is generally higher for passing disease on to children. Nevertheless, in certain countries (e.g. Northern European) children may be also at risk as the patient's partner has higher chance of being a carrier.

6. What are the Ethical, Social and Policy Issues in Population Screening for Hereditary HC?

The central ethical and policy questions are whether the benefits of screening outweigh the costs to a sufficient degree to justify general screening on public health grounds, and whether and how to allow individuals to make informed choices about participating in screening, either for research or therapeutic reasons.

As with any other test for genetic susceptibility, informed consent is considered necessary before beginning the testing process. In addition, whether or not mutation analysis is done, hereditary HC is a genetic disorder, with all the complex information and psychosocial risks that entails. For that reason, it is always recommended that consideration be given to referral to a medical geneticist, a genetic counsellor or a clinician knowledgeable about the genetics of hereditary HC and the concomitant psychosocial issues. The basic areas to be covered in an informed consent discussion are outlined below.

6.1. *Adverse effects of screening*

6.1.1. *Medical effects:* Widespread population-based screening is likely to be associated with direct medical risks. Evaluation of iron overload in individuals with positive screening tests will include liver biopsies and other diagnostic tests associated with adverse effects. Some individuals will be started on venesection treatment, which may also be associated with adverse effects, including mild anaemia and its manifestations. However, the latter can be avoided by monitoring haemoglobin levels.

6.1.2. *Social effects*: An adverse social effect of screening is that increasing social pressure may diminish solidarity and force people to undergo screening although they are not ready for it. Insurance

companies and employers will increasingly be interested in people being screened and will put restrictions on people refusing testing and on people found to be homozygous for the mutations or compound heterozygous, and exclude them from insurance because of a false perception of risks based on genetic testing. These concerns increase if the screening test used generates a high rate of false positive results. This is a form of social stigmatization.

6.1.3. *Confusion:* Patients who participate in genetic screening programmes are commonly confused about the meaning of results. This has occurred when the disorder and tests are relatively simple to understand, as in sickle cell disease, and can be more common when the test or the disorder are genetically complex, as in cystic fibrosis. This confusion can result in decisions (e.g. reproductive decisions) made on the basis of inaccurate information. The incidence of such confusion can, at least in part, be mitigated by the availability of high-quality education and counselling. The availability of such counselling is less likely if screening occurs in primary care settings, where practitioners commonly lack time and knowledge about the genetics or clinical course of hereditary HC. The availability of trained genetic counsellors to provide such services is unlikely if screening occurs in the general population, for a disorder as common as hereditary HC.

6.1.4. *Stigmatization:* Stigmatization refers to a quality of being perceived by others, or by oneself, as being marked in a negative way. Stigmatization is an unwelcome consequence of screening that can occur even when the results are perfectly understood. A concern about the stigmatizing power of genetic information is that such negative self-regard may occur without any actual disease condition; that is, stigmatization may be based solely on genotype not phenotype. Even the most sensitive physician or counsellor will not be able to negate a feeling of stigma in all cases. With regard to hereditary HC, it is possible that some individuals identified as being at risk will suffer from prolonged anxiety or depression, despite the availability of preventive treatment.

6.1.5. *Problems involving disclosure to relatives:* The familial nature of genetic information has ethical implications. Some bioethicists and genetics professionals see a moral obligation on the part of the patient to disclose genetically relevant information to relatives; they may also see a reciprocal obligation on the part of physicians to guide patients in fulfilling this responsibility. From the point of view of the health care provider, two issues are involved: What should one advise one's patients to do about informing relatives, and what obligations does one have oneself? There is no standard practice at this point and inadequate deliberation has been undertaken to weigh the advantages of disclosure, given the familial nature of genetic information, with the principles of privacy and confidentiality with regard to this same information. There are currently few data on the effects within families of disclosure or non-disclosure of genetic information. In addition, physicians might well be concerned about the accuracy of information that patients might pass on. In the United States, this issue has legal aspects as well, with suits brought with regard to physician's obligations to relatives of a proband who are not patients of the physician. Widespread genetic testing for hereditary HC will have to address these issues. Testing will also inevitably uncover unsuspected instances of mispaternity, involving complex questions about concealment or disclosure of confidential information, and adverse consequences in some cases.

6.1.6. *Monetary costs:* The benefits of universal screening are not limited to the potential financial savings, so that benefit/cost calculations should not be the sole determinant of whether screening is justified. Nonetheless, the monetary costs and the potential monetary savings are an important element in determining whether limited health care dollars should be invested in such a programme, particularly if large sums are involved. Costs of screening include: a) Direct medical costs of screening, including blood tests, biopsies, and imaging procedures, and medical complications of biopsies; b) Professional time, including physicians, genetic counsellors, nurses and others, and associated costs of office visits. A critical element in estimating these costs depends on the commitment to pre-test education, counselling, and informed consent.

6.1.7. *Patient education, counselling and informed consent:* A major component in estimating the costs of mass screening hinges on the commitment to informed consent. In some countries, such as the U.S., patient autonomy is a central ethical and legal principle, and it is axiomatic that competent patients should have the opportunity to decide for themselves whether or not to take on tests or procedures. This is particularly important when the test has uncertain risks and benefits, or when reasonable people disagree about how to weigh the relative value of the risks and benefits. If patients are to make informed choices, they need to understand

the relevant facts before testing is done. Since knowledge of hereditary HC is presumably slight among the general public, this would require education about the nature of the disease; the psychosocial risks of testing; the likelihood of becoming ill without testing; the ambiguities of the testing algorithm (false positives, negative predictive value); and the costs and benefits of treatment. The time needed for such education can be considerable, usually beyond the capacity of a primary care office visit. Strategies are therefore needed for other mechanisms for educating potential screenees, such as the use of written material, videos, or interactive computer programmes.

The costs of obtaining meaningful informed consent also depend on decisions about the procedures for obtaining such consent. The cheapest approach utilises an opting-out mechanism (passive consent) in which patients are informed that testing will be done unless they decline. Opting in (or active consent) refers to procedures in which the presumption is that patients will not be tested unless they choose to be tested, presumably after receiving relevant information in a form they can understand. This implies an affirmative obligation for the physician to ensure that such education has been done, along with providing an opportunity for the patient to ask questions. In theory, opt-out mechanisms should have the same standards as opt-in for pre-test education.

In practice, opting-out procedures are typically used when the test or procedure is so clearly beneficial, or has such little potential for risk, that patients can generally be presumed to have little reason to object, and therefore have less need to be informed. Examples include routine tests of little risk, such as pre-operative measurements of haemoglobin concentration for elective surgery.

At the present time, testing for hereditary HC is not in that category, which would argue for high standards of pre-test education and an optional approach.

6.1.8. *Blood donation:* Blood obtained from patients for treatment or prevention of haemochromatosis is sometimes used for transfusion, but in some countries, such as the U.S., the blood is discarded. The latter policy increases the cost to the patients, who may be charged for the procedure, which may have an adverse effect on compliance. If there is no medical justification for the practice, there is also waste of a valuable resource. The panel believes that hereditary HC is not in itself a contraindication to using blood for transfusion or conversion to other products obtained from donated blood, and recommends its use in this way.

7. Is Population Screening Warranted?

The majority of the Panel believes that there is today insufficient evidence to recommend universal, population-based screening for hereditary HC using haematological indices. As far as genetic testing is concerned, the Panel is aware that screening programmes are going to be implemented based on consideration of the high prevalence of the predisposing gene in certain populations. It should be clear that if such programmes were introduced at present, this would be in the absence of good evidence of a favourable benefit from screening. Introduction of screening programmes in the absence of valid research carries the risk of missing the opportunity to determine the effect of screeening. However, if introduced on a service basis, these programmes should be designed in a way that allows the systematic collection of data on implementation, up-take, and operational issues.

Some members of the Panel felt that the lack of evidence from inception cohort studies reporting the course of untreated and treated hereditary HC, and the lack of randomised controlled trials of treatment, should not impede the carrying out of pilot studies of screening for hereditary HC. In certain populations, (particularly where the prevalence of C282Y homozygosity is high and where this is the principal cause of hereditary HC), the introduction of screening programmes clearly linked to the acquisition of informative data including psychological, social and ethical issues might be valuable.

The Panel does *not* recommend testing in children. This position follows that of the United States NIH-DOE Task Force on Genetic Testing, which stated: "Genetic testing of children for adult onset disease should not be undertaken unless direct medical benefit will accrue to the child and this benefit would be lost by waiting until the child has reached adulthood" (21). There is no current evidence to suggest a disease risk that would be ameliorated by diagnosis or treatment in childhood.

8. What are the Research Priorities?

The Panel believes that it should be a priority to conduct population studies that attempt to avoid ascertainment bias in order to establish the overall health impact of hereditary HC. These studies should:

- Determine the prevalence of hereditary HC in defined populations.
- Determine in the same populations the frequency of the heterozygous and homozygous states for C282Y and H63D mutations.
- Derive age-specific penetrance.

- Describe the spectrum of clinical manifestations and the variability of disease progression: this will provide an assessment of age- and sex-specific expressivity.
- Estimate the contribution of hereditary HC to liver disease, hepatocellular carcinoma, diabetes mellitus, arthritis, heart disease and other conditions listed above encountered in the clinical picture of hereditary HC (i.e. estimate the population attributable risks).
- Determine whether homozygotes who do not fulfil the criteria for the diagnosis of hereditary HC may develop any specific morbidity.
- Determine how often heterozygotes have hereditary HC.
- Determine whether heterozygotes (who rarely fulfil the criteria for the diagnosis of hereditary HC) are at increased risk of any specific illness.
- Identify major and minor disease modifiers.

Future Directions

The Panel expressed the view that it would be unethical to conduct a trial that would randomise hereditary HC patients to no treatment. However, information about the course of untreated and treated disease could be obtained from future studies that employ screening methods. These might include cross-sectional studies of the spectrum of disease in a range of patients at different stages of disease, identified through screening programmes. Carefully designed pilot screening programmes which incorporate the follow-up of patients who are identified as having hereditary HC, and matched controls; and studies, such as that being carried out in Busselton, Western Australia, in which archival and current samples are investigated to determine the course of untreated disease.

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