Title:
The cost-effectiveness of genetic screening for hereditary haemochromatosis

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Abstract:
A decision tree model will be created to find the most cost effective method of screening for hereditary haemochromatosis. The perspective of the analysis is NHS perpective. Four techniques are compared with no screening: 1) biochemical screening; 2) gene testing of the proband and spouse if the proband is homozygous (C282Y1/1), if the spouse is heterozygous (C282Y1/2), the children undergo gene testing; 3) Gene testing of the proband; if he or she is homozygous, relatives undergo gene testing; 4) No Screening. Outcome measures used are cost per life-year saved and incremental cost-effectiveness ratio. Initial results seem to indicate that gene testing of the proband and child (if proband is positive) is cost-effective compared to no screening and biochemical screening. The authors would like to develop the work into one with a societal perspective.

Introduction:

Hereditary haemochromatosis (HH) is an autosomal recessive genetic condition in which excess iron is absorbed by the intestine. Individuals with the clinical manifestations of the disease (which include liver cirrhosis, hepatocellular carcinoma, diabetes mellitus, cardiomyopathy and arthropathy) will have accumulated iron over many years of adult life resulting in progressive tissue damage. It is estimated that prevalence of HH in populations of northern European descent is 1:200 to 1:300 [1-3]

HH is unusual among genetic diseases because a simple, effective treatment exists. The disease appears to have a latent, treatable asymptomatic phase (during which time biochemical abnormalities may be present) that can be prevented from deteriorating into serious morbidity. Individuals diagnosed and treated by regular venesection, before symptoms of cirrhosis occur, have been shown to have a normal life expectancy [4]. Once the disease is confirmed in one family member, it may therefore be beneficial to test other family members for the disease. Geneticists and clinicians are still debating the best way to do this.

The discovery of mutations in the *HFE* gene that are present in most HH patients has provided an additional (to transferring saturation and ferritin testing) confirmatory test used for families affected by the disease [5]. Two *HFE* genotypes are commonly associated with haemochromatosis: homozygosity for the C282Y (845A) mutation and compound heterozygosity with the C282Y and H63D (187G) mutation. [5,6,7] Other rarer mutations to *HFE*, in addition to H63D and C282Y, with uncertain clinical significance have also been described.[8].

There have been several attempts to model the cost-effectiveness of different screening techniques [9-19]. The difficulty in getting a straight forward answer on the cost-effectiveness of screening for HH is that the disease penetrance is unknown, yet to achieve any life gains, therapy must start before the complications become too advanced [10,14].

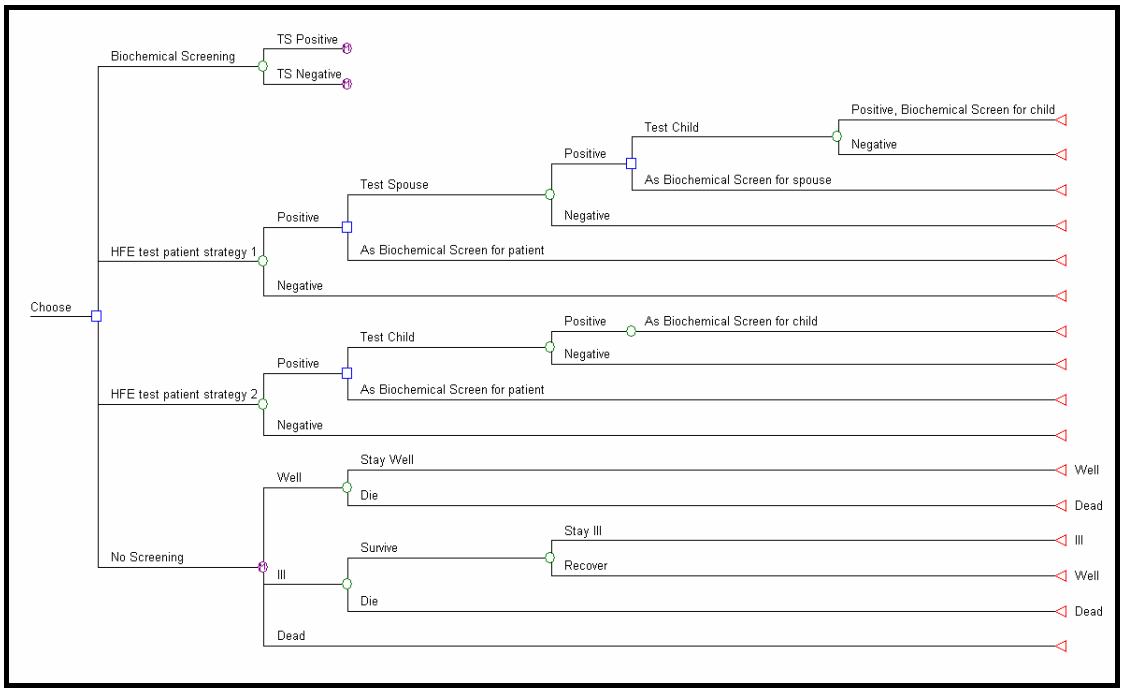
There has yet to be a cost-effectiveness analysis of screening for HH in a UK setting. This paper attempts to use data from a literature review to build a model that compares the cost-effectiveness of 1) Biochemical iron studies, 2) Gene testing of the proband. If the proband is homozygous or compound heterozygous (e.g. C282Y/C282Y), the spouse undergoes gene testing; if he or she carries any mutations, the children undergo gene testing, 3) Gene testing of the proband; if he or she is homozygous, relatives undergo gene testing, and 4) no screening within an NHS perspective.

Methods:

A review of the literature was carried out in order to set model parameters. The search terms were h(a)emochromatosis and cost-effectiveness, cost-benefit, cost-utility, and cost-minimisation. The search was carried out on PubMed and the National Health Service Economic Evaluation Database (NHSEED) and included a limit on time (1985-Present). Additional hand-searching was conducted from the references in the retrieved papers. Expert opinion was sought to verify the model parameters [20,21].

Decision model:
A decision-tree model was built using Treeage Pro (Treeage Pro, version 8.3 Treeage Software Inc. Boston, MA USA 2004). The model attempts to find the most cost-effective strategy for screening for HH, assuming the proband was clinically confirmed to have HH by phenotypic criteria For simplicity, it was assumed that all initial patients had one spouse and one child. The strategies compared were 1) Biochemical screening studies, 2) gene testing of the suspected patient. If the patient is homozygous or compound heterozygous (e.g. C282Y/C282Y), the spouse undergoes gene testing; if he or she carries any mutations, the children undergo gene testing (HFE testing strategy 1), 3) gene testing of the patient; if he or she is homozygous, relatives undergo gene testing (HFE testing strategy 2), and 4) no screening within an NHS perspective. Biochemical screening is current practice for patients suspected of HH, and having two methods of genetic screening is to try and find the most cost-effective screening strategy. A simplified version of the model is presented in Figure 1. The squares are decision nodes, empty circles chance nodes, circles with M indicate Markov processes, and finally triangles are terminal nodes. In the Biochemical Screening arm, the Markov processes are the same as illustrated in the No Screening arm. The gain of Quality Adjusted Life-Years (QALYs) was used as an outcome measure.

Figure 1: Simplified Decision Tree



Biochemical Studies
In the biochemical studies branch of the tree, the patient undergoes no genetic testing, but is subjected to Transferrin-iron saturation (TS) and serum ferritin testing. Several studies have found that transferrin saturation might be elevated by age 10 and would usually present by age 40 [22,23,24]. We assumed that patients at high risk who tested negative in the initial screening would be tested regularly at 5 year intervals. Children would be in the Markov processes for 5 cycles longer, given they start

screening at an earlier age. Therefore, the Markov cycle was 5 years, with sensitivity analysis ranging from 1-10 years. The probability of testing positive was assumed to be an exponential function with an upper limit of 4% of the population screened being positive.

HFE gene testing strategy 1
The first of the gene testing strategy is a type of cascade testing. If the suspected HH patient undergoes genetic testing and the result is positive, then the spouse undergoes testing, then the child if that result is positive. All individuals who test positive will undergo a biochemical screen as described in the Biochemical Screening arm. If the spouse/child genetic test is negative, they are assumed to go into the no screening arm. Children will only be tested if both the patient and the spouse are homozygous. The probability of the child being homozygous was assumed to be 50%.

HFE gene testing strategy 2
The second strategy is similar to the first, but the spouse does not undergo gene testing. The child expected probability is therefore assumed to be population risk.

Assumptions
Key assumptions for the model are laid out in Table I. The authors assumed that the probability of death for people who were non-HH or HH but non-cirrhotic to be .02 for simplicity. To calculate the probability of dying in the next year for people with cirrhotic HH and those without HH or non-cirrhotic HH we followed the methodology set out in Åsberg, et al [25]. We use predicted age specific death rates from the year 2003 from the National Statistics Office for England and Wales [26]. We assumed that venesection was the treatment used for those with confirmed (and/or latent) HH and that cirrhosis was treated with courses associated with that disease.

We assumed the base rate for the UK population prevalence of HH was .003, similar to that of other populations of northern European descent [11, 27]. The sensitivity and specificity of the biochemical tests (TS and SF) were assumed to be .96 [28]. The genetic test was assumed to have a specificity and sensitivity of .99. Venesection success rate was based on published evidence [8-15, 25]. The Quality of Life (QoL) estimates were based on expert opinion [Jennings, Willis] and from [25].

The excess mortality in HH is usually associated with liver cirrhosis, heart failure, and diabetes [1]. Åsberg, et al [28]and Beutler, et al [6] found that there was not an increased prevalence of cardiac disease and diabetes in phenotypic or genotypic screened HH persons. Given that, and that most HH diabetes patients also have liver cirrhosis [1, 29], we have taken liver cirrhosis (and its complications) to be the single factor influencing mortality. This is similar to the methodology set out in Åsberg, et al [25].

Utility estimates are based on Åsberg, et al[28]. We assumed that people would enter one of three states: ‘well’, ‘ill’, and ‘dead’. Dead was considered an absorbing state. For simplicity, if relatives (spouse and/or child) tested negative for the HFE mutation, they were ‘lost’ to the model, and were treated as a one off cost and utility gain. See discussion for more on utility estimates.

Table I: Base case values for the model		
Variable	Base case	Range for sensitivity analysis
Prevalence of HH	.003	.001-.008
Sensitivity of Biochemical tests (TS and SF)	.962	.85-.99
Specificity of Biochemical tests	.96	.85-.99
Sensitivity of HFE test	.99	.90-1.00
Specificity of HFE test	.99	.90-1.00
Patients compliant with venesection	.80	.50-1.00
QoL for patients in 'well' state	1	.9-1.00
QoL for patients in 'ill' state	.95	.80-1.00
QoL for patients in 'dead' state	0	0

Cost:
Costs are expressed in UK£. Future costs are discounted at 3% [30]. Where prices were in US$, prices were converted to 2004 prices using the OECD PPP mechanism. The cost perspective is that of the NHS. Where cost data was not available from the NHS, literature and expert opinion was used. Table II shows the unit costs included in this analysis. Sensitivity analysis was carried out on all cost elements.

The cost of the 'well' state included all relevant costs from each arm. The cost of the 'ill' state of the Markov model was calculated by using an average yearly cost of cirrhosis care, plus the appropriate costs for each arm of testing. The cost of 'dead' included the relevant costs from each arm.

Table II: Unit Costs (UK£)		
Cost Item	Unit Cost (sensitivity analysis range)	Source
HFE gene test	110 (50-160)	10,11,15,25
Genetic Counselling	To be included in final costings	
Biochemical Screening tests (Serum Ferritin and Transferrin saturation	18 (9-27)	10,11,15,25,31
Specialist physician – initial consult	40 (30-50)	31
Specialist physician – subsequent consult	20 (10-30)	31
Day admission to hospital	262 (200-350)	31
Outpatient appointment	67 (50-80)	31
Venesection – one session	29 (15-45)	10,11,15,25,31
Annual Cost-Cirrhosis	1610 (500-15000)	10,15,25

Results
Table III gives the results of the model. Not screening was not cost-effective when compared with any of the strategies. Current practice, biochemical screening, seemed to be more cost effective than No Screening and HFE testing strategy 1. HFE testing strategy was only cost-effective when compared with no screening. HFE Testing

strategy 2, that of testing the suspected patient and child, would be the most cost effective when compared to the all other interventions.

Table III: Model Results

Intervention	Cost (£)	Effectiveness (QALYs Gained) *	Incremental Cost/QALY**
No screening	584	0	-
Biochemical Screening	793	5	159
HFE Testing strategy 1	3370	18	198
HFE Testing strategy 2	2307	16	138

*For entire family.
**All numbers rounded to nearest whole number.

Sensitivity analysis
Table IV shows the initial results of the sensitivity analysis. Initial sensitivity analysis shows that cost-effectiveness is sensitive to the cost of the genetic test, with biochemical screening becoming more cost-effective when tests cost £150. Both genetic testing strategies become cost-effective in comparison to biochemical screening when test cost is below £50.

The model does not seem to be sensitive to the cost of TS testing. HFE testing strategy 2 is still more cost-effective than biochemical screening. This is not necessarily surprising, given that all the active screening strategies depend on TS testing at some point.

The model seems to be sensitive to cost of illness. When the cost of illness is upwards of £15000, both of the genetic testing strategies have a lower ICER than Biochemical screening. However, this relationship only seems to be one-way, as the lower the cost, biochemical screening has a lower ICER than HFE strategy 1.

Additional sensitivity analysis will be carried out on utility.

Table IV: One Way Sensitivity Analysis (Incremental Cost/QALY)

Cost of Gene Test (£)	**£50**	**£110**	**£150**
No Screening			
Biochemical Screening	159	159	159
HFE Strategy 1	169	198	216
HFE Strategy 2	114	138	152
Cost of Transferrin Saturation test (£)	**£10**	**£18**	**£26**
No Screening			
Biochemical Screening	138	159	179
HFE Strategy 1	179	198	217
HFE Strategy 2	123	138	152
Cost of Illness (£)	**£500**	**£1610**	**£15000**
No Screening	276	292	484
Biochemical Screening	144	159	339
HFE Strategy 1	185	198	348
HFE Strategy 2	124	138	251

Discussion:

This paper is very much a work in progress. The evidence has not been systematically reviewed yet, but it is the plan of the authors to do so. This may affect our assumptions and the choice of model.

It seems that our model shows that the use of the HFE genetic test to identify and treat HH patients is a cost-effective strategy when compared to no screening, or the use of biochemical (TS) tests. Whether or not it is worthwhile to the NHS is dependant on the costs and benefits when compared to other health-care activities. In our initial sensitivity analysis, the model seems to be sensitive to the cost of the genetic test, and the cost of illness.

Our assumptions on utility are derived from one source, and we feel need closer scrutiny. Given that most utility gains from the genetic testing strategies will derive from faster diagnosis (and thus avoiding illness by early treatment) for a HH patient, it is very important to attach accurate utilities to the Markov states of 'Well' and 'Ill'. It would be helpful and interesting to study the quality of life literature for patients suffering from cirrhosis, diabetes, and heart failure to try to gauge the utility gained from avoiding these diseases. Even so, the penetrance of these illnesses within HH patients is as yet unknown. Therefore, it is difficult to attach utilities to the state of 'Ill' in particular. For example, knowing one is ill without any symptoms could lead to both gains and reductions in utility, depending on personal preferences.

The costs included in the model are limited at this time, while we continue to gather data from both literature and expert opinion. Including full costs of all arms of screening will hopefully give a more accurate picture of what is the best method. We intend to carry out a societal approach so have not included indirect costs, such as productivity losses to the patient, differences in career/life choices for patients who are diagnosed or test free of the disease. While this is of interest to the authors, it is beyond the scope of this paper.

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