Screening for hereditary hemochromatosis in siblings and children of affected patients: a cost-effectiveness analysis
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Four screening strategies for hereditary haemochromatosis in siblings and children of affected patients were investigated.

1. Serum iron studies.
2. HFE gene testing of the proband. If the proband was homozygous for mutation of the HFE gene (C282Y+/+), the spouse underwent gene testing. If the spouse was heterozygous (C282Y+/-), the children underwent gene testing.
3. Gene testing of the proband. If the proband was homozygous, relatives underwent gene testing.
4. Direct gene testing of the relatives. Relatives means children and siblings. Iron studies were conducted for all those who tested positive for C282Y+/+. The proband would only be gene tested if all relatives gene-tested negative.

All those who gene-tested positive would be tested for serum iron. For siblings, this was either performed once or repeated until the iron level was normal. For children, this was modelled. The treatment for iron overload and hereditary haemochromatosis was by phlebotomy. For "true positives" (gene and iron tested positive), children would receive maintenance therapy (3 times annually) and siblings would receive an initial set of 40 phlebotomies followed by maintenance. The "false positives" (iron overload, but genetic negative) would receive 5 phlebotomies.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised siblings and children of an affected proband with hereditary haemochromatosis.

Setting
The setting was the community. The economic analysis was carried out in the USA.

Dates to which data relate
The effectiveness evidence, resource use and cost parameters were derived from studies published between 1994 and 1999.

Source of effectiveness data
The effectiveness data were derived from a review of completed studies and assumptions made by the authors.
Modelling
A decision model was applied to determine the most cost-effective screening strategy for hereditary haemochromatosis in siblings and children of an affected proband. A Markov model was used to model the repeated iron studies in children under different screening methods. This included three states: the initial screening, from which patients could go to either test positive or test negative. The cycle length in the base-case was 5 years.

Outcomes assessed in the review
The outcomes assessed in the review were:

- the prevalence of C282Y+/+ among patients with phenotypic evidence of hereditary haemochromatosis;
- the proportion of people with hereditary haemochromatosis who had elevated transferrin saturation or ferritin levels; and
- the proportion of those who would develop organ damage (cirrhosis, diabetes mellitus, heart failure), and their incidence and associated life expectancy.

Study designs and other criteria for inclusion in the review
Not reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Nine references were cited in the study.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The prevalence of C282Y+/+ among patients with phenotypic evidence of hereditary haemochromatosis was 90% in the USA.

The proportion of people with hereditary haemochromatosis who had elevated transferrin saturation or ferritin levels was approximately 80%. The proportion of those who would develop organ damage (cirrhosis, diabetes mellitus, heart failure) was 50%.
The probability of developing complications was 30% for cirrhosis, 20% for diabetes mellitus, 5% for heart failure, 12% for all of the above, 9% for heart failure and cirrhosis, 4% for heart failure and diabetes, and 20% for cirrhosis and diabetes.

The proportion of hepatocellular carcinoma among cirrhotic patients was 25%.

The life expectancy associated with different conditions was 79 years for people without hereditary haemochromatosis, 69 years for persons with cirrhosis, 66 years for persons with hepatocellular carcinoma, 70 years for persons with diabetes mellitus, and 57 years for persons with heart failure.

Methods used to derive estimates of effectiveness
The authors made assumptions to supplement some of the reviewed evidence in the decision model.

Estimates of effectiveness and key assumptions
The authors made the following additional assumptions.

The genetic test was assumed to have been performed once only.

The prevalence of hereditary haemochromatosis was assumed to be 10%.

The frequency of screening children using iron studies was assumed to be every 5 years, from the age of 10 to 30.

The sensitivity of serum iron studies for diagnosing hereditary haemochromatosis was 98%.

The specificity of serum iron studies for diagnosing hereditary haemochromatosis was 96%.

The age of first symptoms of complications was assumed to be 55 years.

The early diagnosis and treatment was assumed to ensure normal life expectancy.

Equal sex distribution was assumed in the screening pedigree.

The prevalence of heterozygotes was assumed to be 10% among white persons.

Patients with iron overload and hereditary haemochromatosis underwent phlebotomy until the iron levels were reduced to normal.

Measure of benefits used in the economic analysis
The outcome was estimated in life-years gained. The benefits were discounted at an annual rate of 3%.

Direct costs
The costs of treating different complication were obtained from published studies. The annual cost was $2,500 for cirrhosis, $1,500 for diabetes care, $50,000 for hepatocellular carcinoma, and $45,000 for heart failure in the year preceding death. The cost of iron studies was derived from the United Physicians Association at the University of New Mexico Health Sciences Centre, and was $85. The cost of gene testing was based on a quote given by SmithKline Beecham Laboratories, and was $173. The cost of a phlebotomy was $50 per session. The costs were discounted at a rate of 3% per year. The quantities of resources calculated by the model were not stated.

Statistical analysis of costs
No statistical analysis of the costs was reported.
Indirect Costs
No indirect costs were considered in the analysis.

Currency
US dollar ($).

Sensitivity analysis
One-way and two-way sensitivity analyses were performed to measure the effect on the incremental cost-effectiveness ratio, relative to no screening. The cost of gene testing was varied between $191 (SmithKline Beecham Laboratories cost with additional test for H63D mutation) and $85. The cost of measuring serum iron transferrin saturation and serum ferritin was varied from $85 to $40. The proportion of patients with haemochromatosis, in whom the HFE gene testing was positive for C282Y+/+ mutation, was varied between 60 and 100%. The sensitivity and specificity of iron studies were varied between 90 and 100%. The frequency of serum iron studies in children was reduced to every 10 years. The prevalence of the C282Y+/- mutation in the population was varied between 1 per 1,000 persons to 20 per 1,000 persons.

Estimated benefits used in the economic analysis
The authors only reported the benefit for the strategy of no screening (discounted at 3% annually) separately. The discounted life expectancy was 39 years for children and 65.5 years for siblings.

Cost results
The cost results according to strategy were only presented in a graphical form (cost versus the number of children or siblings screened).

The cost of screening two children and two siblings was $4,110 when using iron studies, and $3,309 when using genetic testing. The costs were discounted at an annual rate of 3%.

Synthesis of costs and benefits
Incremental analyses were only performed for the screening alternatives versus the ‘no screening’ alternative. The estimated benefits and costs were combined into incremental cost-effectiveness ratios (ICERs). However, these ratios were not given according to the screening strategy for the whole at-risk population. Instead, they were presented separately for children and siblings according to the number of individuals in the pedigree. Also, the results were not fully reported.

The strategy of HFE gene testing of the proband, followed by testing of a child, was stated to be the most cost-effective strategy to screen one child at an ICER of $508 per life-year saved.

For screening two or more children, the strategy of gene testing the spouse if the proband was found to be homozygous was stated to be the most cost-effective. For example, screening two children had an ICER of $3,665 per additional life-year saved, whereas screening using serum iron studies had an ICER of $7,934 per life-year saved and the strategy in which children were gene tested before the proband had an ICER of $12,277 per life-year saved.

For siblings, all screening strategies were dominant compared with no screening. Screening with serum iron studies was the most expensive screening strategy throughout. Of the two strategies that used HFE gene testing, gene testing of the siblings first resulted in lower costs when only one sibling was screened. However, for two or more siblings, HFE gene testing of the proband first was less costly.

The results were stated to be sensitive to the proportion of patients with phenotypic haemochromatosis in whom the HFE gene test was positive for C282Y+/+, and to the cost of gene testing. When this proportion was increased to 100%, then testing the genes of the relatives before the proband was a less expensive strategy for screening siblings and one
child. If the cost of genetic testing decreased to less than $95, the strategy of HFE gene testing of the siblings and the spouse, followed by the children where indicated, became less expensive than iron studies.

Authors' conclusions
HFE gene testing for the C282Y mutation was a cost-effective method for screening the relatives of patients with hereditary haemochromatosis.

CRD COMMENTARY - Selection of comparators
The choice of alternatives for the comparison was justified on the grounds that they were available treatment options for patients with phenotypic hereditary haemochromatosis. When comparing different screening alternatives with no screening, it was unclear whether 'no screening' represented the current practice. A more fundamental problem was that the incremental analysis always compared strategies to no screening. This is incorrect and misleading in that it does not account for the increments between the strategies. The comparator should always be the next most expensive or effective strategy.

Validity of estimate of measure of effectiveness
The authors used evidence from published studies. However, they did not present sufficient detail to enable the appropriateness of the data sources to be discussed. Some of the authors' assumptions were not explicitly justified and no references were provided. The impact of some of the estimates was investigated by sensitivity analyses, but the ranges used were not adequately justified.

Validity of estimate of measure of benefit
The estimation of the benefits was modelled. The instrument used to derive the measure of life-years saved, a decision modelling framework, was appropriate. Unfortunately, very few results were given. This reduced transparency and the applicability to decision-making. Similarly, the results for the ICERs were incompletely reported, making the sensitivity analysis difficult to interpret.

Validity of estimate of costs
Although the authors reported that the costs were estimated from a societal perspective, the indirect costs were not explicitly included. Also, it is unclear whether the indirect costs were included in some of the unit costs used. The authors seem to have included all the costs relevant to the hereditary haemochromatosis condition and screening. The total costs were estimated using a decision model. Unfortunately, very few cost results were given. The costs that were given were mainly presented graphically. This reduced transparency and the applicability to decision-making. Sensitivity analyses were conducted for some of the unit costs and quantities of resource use. The unit prices were derived from published studies and tariffs. The authors appropriately discounted the annual costs. It is unclear whether the prices related to the same price year.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. The issue of generalisability was addressed, and the authors stated that the results are not generalisable to the general public. Some limitations of the study were reported. These included the variable phenotypic expression of the hereditary haemochromatosis (possibly not well located by the phenotypic criteria employed), and the potential for unnecessary anxiety, stigma or discomfort.

Implications of the study
The authors acknowledge the need for further studies to examine the ethical, legal, and social implications of genetic testing among asymptomatic persons. There are serious problems with the incremental analysis and a lack of transparency in the results. The make the authors’ claims relating to the cost-effectiveness questionable.
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