Diagnostic strategies using DNA testing for hereditary haemochromatosis in at-risk populations

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

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Executive summary

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Executive summary

Background

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

Objective

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

Methods

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

Data sources

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

Study selection

Studies were included if they fulfilled the following criteria:

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

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

Data extraction and quality assessment

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

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

Data synthesis

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

Economic model

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

Results

Number and quality of studies

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

Summary of clinical validity and clinical utility

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

Summary of psychosocial aspects of DNA testing

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

Summary of economic evaluation

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

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

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

Conclusions

Implications for service provision

The preferred strategy in practice is DNA testing in conjunction with testing iron parameters when there is a clear clinical indication of suspicion of risk for haemochromatosis because of biochemical criteria or when there is a familial risk for hereditary haemochromatosis. Although clinical practice among those expert and interested in the management of the condition is already thought to follow this strategy, the development and dissemination of guidelines to physicians in both primary and secondary care is advisable.

Access to genetic testing and centralisation of test provision in expert laboratories would lower the cost of testing, improve the cost-effectiveness of the strategy and improve the quality of information provided to clinicians and patients.

Suggested research priorities

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

Publication

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The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

Second, the HTA programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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

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

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