Will genetic testing alter the management of disease caused by infectious agents: a cost-effectiveness analysis of gene-testing strategies for prevention of rheumatic fever

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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
The screening of all children at birth for genetic susceptibility to rheumatic fever (RF) was investigated. For the group that would test positive for RF high-risk genotype, monthly or daily prophylaxis would be given for the primary prevention of RF. For the remaining children who tested negative for the RF high-risk genotype, pharyngitis would be treated with the usual standard of care. For any individuals who developed RF (regardless of genotype), standard monthly or daily prophylaxis would be given. This intervention was compared with no genetic testing and the provision of usual prophylaxis for pharyngitis and RF.

Type of intervention
Screening.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical 2000 national birth cohort.

Setting
The study setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies dating from 1954 to 2000. The price year was 1999.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies, and from unpublished data from national sources.

Modelling
To estimate the cost-effectiveness of genetic screening for RF risk, the authors developed a decision analysis model to compare the two RF prevention strategies. The model evaluated the outcomes and costs on an annual basis to the age of 75 years. The model was a Markov model, in which the risk of streptococcal infection was calculated on an annual basis. In the Markov node, the yearly outcomes were no infection, streptococcal pharyngitis (SP) with no sequelae, asymptomatic valvarul heart disease, symptomatic valvarul heart disease, or death. Once established, chronic RF-associated heart disease could lead to the development of endocarditis or congestive heart failure in later years, which could possible require valvular surgery or result in death.
Outcomes assessed in the review
The outcomes assessed included:

- the prevalence of high-risk genetic susceptibility;
- the specificity and sensitivity of the test;
- the age-dependent incidence of SP per patient-year;
- the incidence of acute RF following SP;
- the net incidence of acute RF among high-risk individuals receiving prophylaxis, per patient-year;
- the probability of death within 1 year;
- the probability of rheumatic heart disease (RHD) in individuals with acute RF;
- progression from mild RHD to RHD with congestive heart failure (CHF);
- the annual risk of endocarditis in individuals with RHD;
- the annual risk of hospitalisation with severe RHD per person-year for individuals with RHD with CHF;
- the improvement to class III or better, and the risk of death in patients with RHD with CHF; and
- the failure of medical therapy to cure, the requirement for surgery, and the risk of death for individuals with infective endocarditis.

Study designs and other criteria for inclusion in the review
Estimates of genetic susceptibility were derived from HLA and B cell marker studies of RF susceptibility. For the general low-risk population, age-dependent SP attack rates were derived from a prospective community study, and model results were compared with the cumulative risk of RF reported from the Framingham Study (see Other Publications of Related Interest). Attack rates for high-risk individuals were derived from prospective studies of the incidence of pharyngitis and the rate of recurrence of RF among patients with a prior history of RF. The probability of death due to acute RF and that of progression to chronic valvular heart disease or CHF were derived from a prospective cohort study, a cross-sectional study and a case series. Estimates of the efficacy of antibiotic prophylaxis for the prevention of RF were obtained from controlled trials of penicillin and sulfonamide regimens. The risks of complications due to rheumatic valvular heart disease and death associated with medical and surgical therapy were derived from references and reviews.

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
When estimates derived from the review were imprecise, the authors chose starting values for the base-case that would tend to bias results against the gene-testing option.

Number of primary studies included
Nineteen studies were included in the review.

**Methods of combining primary studies**
Not reported.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
The prevalence of high-risk genetic susceptibility was 10%.

The sensitivity of the test was 90% and the specificity was 95%.

The age-dependent incidence of SP per patient-year was 0.3 to 20% among patients not receiving prophylaxis, and 0.3 to 8.5% among high-risk patients receiving prophylaxis.

The incidence of RF following SP was 0.39% among the general population and 5% among high-risk patients.

The net incidence of acute RF per patient-year was 0.4% among high-risk individuals receiving prophylaxis.

For individuals with RF, the probability of death within one year was 0.1% and the probability of RHD was 50%.

For individuals with RHD, progression from mild RHD to CHF was 0.1 to 2% per patient-year, and the annual risk of endocarditis was 0.8%.

For individuals with RHD with CHF, the annual risk of hospitalisation with severe RHD was 35% per patient-year. The improvement to class III or better was 68% with medical therapy, 96% with early surgical therapy, and 70% with late surgical therapy. The risk of death was 43% with severe decompensated CHF, 3% with early surgical therapy and 25% with late surgical therapy.

For individuals with infective endocarditis, the failure of medical therapy to cure was 5%. The requirement for surgery was 22% if progression to CHF, and 3% with persistent infection. The risk of death was 1.5%.

**Measure of benefits used in the economic analysis**
The measure of benefits used was the quality-adjusted life-years (QALYs). Utilities for the different health states (i.e. no infection, SP, acute RF, recovered RF, chronic valvular disease, and compensated and decompensated CHF) were assigned on the basis of data from published studies. The studies assessed the quality of life of patients with similar mild respiratory conditions and those with mild, moderate and severe chronic respiratory diseases.

**Direct costs**
The direct costs included in the analysis were those of the health care system and of the relatives of the patient. The medical care costs included were for genetic testing, prophylaxis, SP-related care, the admission and subsequent care of patients with acute RF, mild CHF-related care, care for infectious endocarditis without valve replacement, severe CHF-related care, and RHD-related admission and valvular repair for CHF or endocarditis. The non-medical care costs covered home care for a child with pharyngitis or RF. The cost of genetic testing was derived from unpublished data from the University of Cleveland Hospitals. All other medical costs were derived from Medicare reimbursements for diagnosis related-groups (DRGs) and relative value unit-based physician charges based on the average length of hospitalisation for each DRG. The cost of home care for a child with pharyngitis or RF was calculated from the time lost from work and the parent's wage rate.

The costs and resource use were not reported separately, although the authors did break down the costs by type of
resource use. Discounting was relevant as all the costs were incurred during a 75-year period. Hence, discounting was appropriately performed at a rate of 3% per annum. The study reported the average costs. All the costs were adjusted to average price levels for 1999, using the Consumer Price Index for All Urban Consumers.

**Statistical analysis of costs**
The costs were treated as point estimates (i.e. the data were deterministic).

**Indirect Costs**
The indirect costs were not included.

**Currency**
US dollars ($).

**Sensitivity analysis**
To estimate the general application of the decision analysis, the authors examined variation in several parameters. These parameters included the cost of genetic testing, the prevalence of genetic susceptibility to acute RF, and the sensitivity and specificity of genetic testing. Also examined, were the costs of treatment for SP, RF prophylaxis, acute RF without sequelae and RF with valvular complications, the probability of RF following SP in high-risk patients, and the discount rate.

**Estimated benefits used in the economic analysis**
The incremental life-years added per 1,000 population when using the screening strategy over no screening were 120.

The cumulative RF cases expected per 1,000 population were 35 with the screening strategy and 49 with no screening.

The incremental discounted QALYs gained per 1,000 population using the screening strategy over no screening were 80.

**Cost results**
The cost of RF-related care per person was $9,735 when using the screening strategy and $9,103 when using no screening.

**Synthesis of costs and benefits**
The costs and benefits were combined by calculating a cost-utility ratio (additional cost required per QALY gained). The cost-utility ratio of the screening strategy over no screening was $7,900 per QALY gained. The results of the sensitivity analysis showed that genetic screening became the dominant strategy (i.e. more effective and less expensive than no screening) if the specificity of the test was at least 98%, the annual cost of prophylaxis was less than $550, or the annual cost of caring for an individual with severe RHD increased to over $32,000.

In a more speculative analysis, the authors examined the potential impact of adopting a strategy of not treating uncomplicated SP in low-risk patients. The cost-savings generated by this strategy would then provide an economic advantage to gene testing, unless the cost of testing was more than $380, the yearly cost of prophylaxis was over $800, or the proportion of high-risk individuals in the population was below 4.5%.

**Authors' conclusions**
The decision analysis indicated that, with current prevention strategies and available screening technology, genetic testing for susceptibility to rheumatic fever (RF) could prove cost-effective in the USA.
CRD COMMENTARY - Selection of comparators

Although no explicit justification was given for using a no screening strategy as the comparator, it would appear to represent current practice in the authors' setting. You should decide if the comparator used represents current practice in your own setting.

Validity of estimate of measure of effectiveness

The authors did not explicitly report that a systematic review was undertaken to identify relevant research and minimise biases, and they did not report the sources searched to identify evidence. However, it would appear that an extensive review of the literature was undertaken since both published and unpublished data were included. The authors satisfactorily reported all the study designs used in the literature considered in the analysis. Five of the 19 studies included in the review dated before 1970, and it is unclear whether the results of these studies still hold in current settings. When a base estimate of effectiveness was derived from multiple studies, the authors did not report how the results from the different studies were combined (if at all), or whether any differences between these studies were investigated. However, they did report that, if the estimate measures were uncertain, the value that tended to bias against genetic testing was used in the base-case scenario. Further, the authors appropriately varied measures of effectiveness in the sensitivity analysis, using the ranges reported in the rest of the literature.

Validity of estimate of measure of benefit

The estimation of benefits was modelled. The authors did not report the instruments used in the literature to derive measures of quality of life.

Validity of estimate of costs

The authors reported that the costs were estimated from a societal perspective, but the indirect costs (i.e. productivity losses associated with mortality and morbidity) were not included in the analysis. The omission of this cost category would probably bias the results in favour of no screening, as screening increased both life expectancy and quality of life. However, all relevant direct medical and non-medical costs appear to have been included in the analysis. The costs and the quantities were not reported separately, which will limit the generalisability of the authors’ results, but the costs were reported for each level of resource use. The unit costs were derived from unpublished sources and Medicare reimbursement charges. A sensitivity analysis of the prices was appropriately conducted, using ranges that appear to have been appropriate. As all the costs were incurred over 75 years, discounting was relevant and was appropriately performed. Medicare charges were used to proxy prices, which will not reflect the true cost of providing the service. The price year was reported, which will ease any possible inflation exercises.

Other issues

The authors did not compare their results with those from other studies, as it would appear that their study was the only one assessing the use of genetic testing for the prevention of RF. The issue of generalisability to other settings was appropriately addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors reported that their model included several simplifications. First, the model did not consider the effects of other streptococcal infections on the costs or quality of life. Second, the model did not consider the side effects of antibiotic therapy, such as fungal overgrowth or bacterial resistance. The authors reported that an assessment of the potential impact of prolonged treatment with penicillin in a large segment of the population, which might hasten the spread of resistant organisms, was beyond the scope of their analysis.

Implications of the study

The authors reported that, for testing to be most efficient, careful attention to test development is needed so that test accuracy is optimised and the costs are limited. The authors stated that they expect similar strategies focusing on enhanced primary or secondary prophylaxis, according to knowledge of genetic testing, could also serve to limit disease caused by other chronic and recurrent infections.
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