Cost-effectiveness of thiopurine methyltransferase genotype screening in patients about to commence azathioprine therapy for treatment of inflammatory bowel disease
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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 study investigated the screening for thiopurine methyltransferase (TPMT) gene polymorphisms prior to the initiation of azathioprine therapy in the management of inflammatory bowel disease (IBD). A polymerase chain reaction was used for testing for TPMT.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The population comprised a hypothetical cohort of 1,000 patients suffering from IBD who were treated with azathioprine and who underwent standard haematological monitoring.

Setting
The setting was unclear. The economic study was carried out in Glasgow, Scotland, UK.

Dates to which data relate
The effectiveness data were gathered from studies published between 1989 and 2003. The dates to which the resource use data related were unclear. The price year was not stated.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of published studies.

Modelling
A model was used to evaluate the cost-effectiveness of screening for TPMT polymorphisms prior to the initiation of azathioprine therapy. A lifetime horizon was used. Details of the model were limited, although a visual depiction was provided.

Outcomes assessed in the review
The outcomes assessed were the frequency of leucopenia in patients receiving thiopurine drugs and the risk of leucopenia association with TPMT deficiency.
Study designs and other criteria for inclusion in the review
All the studies used to assess the frequency of leucopenia were retrospective studies. One study used to assess the risk of leucopenia association with TPMT deficiency was a cohort study.

Sources searched to identify primary studies
MEDLINE was searched from 1989 to present, to identify case series that reported the frequency of severe leucopenia in adults with IBD treated with azathioprine, or its metabolic product mercaptopurine. Relevant referenced studies were also examined.

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

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

Number of primary studies included
Eight studies were included in the analysis.

Methods of combining primary studies
An overall frequency of leucopenia was derived from the results of seven studies. The authors combined the results of two studies to assess the risk of leucopenia association with TPMT, and applied a 95% confidence interval (CI) to cover the potential range.

Investigation of differences between primary studies
The authors did not report whether they had investigated differences between the primary studies.

Results of the review
The overall frequency of leucopenia was 3.2%.

The risk of leucopenia association with TPMT was 32% (95% CI: 20 - 47).

Methods used to derive estimates of effectiveness
The authors derived estimates of effectiveness from the model and assumptions.

Estimates of effectiveness and key assumptions
Based on the model, the absolute risk of leucopenia was 100% in homozygotes, 6.4% (95% CI: 2.7 - 11) in heterozygotes and 2.5% (95% CI: 1.9 - 2.9) in the wild-type population.

The relative risk of leucopenia was 31 in homozygotes, 0.78 (95% CI: 0.59 - 0.9) in heterozygotes and 2 (95% CI: 0.84 - 3.52) in the wild-type population.

Based on the model, the sensitivity was 31%, the specificity 89%, the positive predictive value 9% and the negative predictive value 97%.

Based on the assumption that homozygotes would not receive azathioprine, and that heterozygotes would receive a reduced dose and therefore avoid myelotoxicity, the number-needed-to-screen (NNS) to avoid one adverse event was
The authors proposed as a conservative estimate that one death per 1,000 patients would be avoided if those with absent TPMT activity were identified by screening and either avoided azathioprine or received a much lower dose.

**Measure of benefits used in the economic analysis**
The measure of benefit used was the number of years of life saved. This was calculated on the basis of the authors' assumption that screening would avoid one death per 1,000 patients. Life expectancy in Scotland was derived from current statistics from 2001. The health benefits were reported undiscounted, but a discount rate of 1.5% per year was used to calculate the cost-effectiveness ratio.

**Direct costs**
The direct costs considered were those of the health service. These included the costs of testing and the cost of morbidity (including outpatient visits and hospital stay). It appears that the costs have been estimated using actual data. The resource use quantities and the costs were reported separately. The authors assumed that two thirds of patients suffering significant leucopenia could be managed as outpatients. The cost of a 10-day stay in a haematology ward was used to assess the cost of hospital stay. The costs were obtained from the Information and Statistics Division of the Common Services Agency in Scotland. The price year was not reported. It was unclear whether the costs were discounted using the same discount rate as that used for the health benefits (1.5% per year). The authors reported the total cost and cost per patient.

**Statistical analysis of costs**
The costs were treated deterministically. No statistical analysis of the costs was undertaken.

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

**Currency**
UK pounds sterling (£).

**Sensitivity analysis**
The upper and lower bounds of the 95% CIs for association rate were used.

**Estimated benefits used in the economic analysis**
The number of life-years saved (LYS) was 47 for a 30-year-old patient and 20 for a 60-year-old patient.

**Cost results**
The net cost of avoiding morbidity by screening 1,000 patients was 16,330 (£, or 1,633 per patient).

**Synthesis of costs and benefits**
The cost per LYS was 347 for a 30-year-old patient and 817 for a 60-year-old patient.

Applying the 95% CI for association rate, the cost per LYS was between 162 and 448 for a 30-year-old patient and between 380 and 1,052 for a 60-year-old patient.

When discounting at 1.5%, the cost per LYS was 487 (95% CI: 227 - 627) for a 30-year-old patient and 951 (95% CI: 433 - 1,532) for a 60-year-old patient.
Authors’ conclusions
"Screening for TPMT (thiopurine methyltransferase) genotype is an acceptable and cost effective intervention in the management of patients with IBD (inflammatory bowel disease) requiring therapy with azathioprine. However, screening should be viewed as an adjunct to standard haematological monitoring and not as a replacement."

CRD COMMENTARY - Selection of comparators
The comparator to screening for TPMT gene polymorphisms was no screening. This choice was explicitly justified, as it represents the choice that gastroenterologists face: whether or not to screen for susceptibility. In addition, no screening strategy allows the active value of screening to be evaluated.

Validity of estimate of measure of effectiveness
Several published studies were used to obtain the input parameters. A systematic review of the literature was undertaken to identify all relevant research and to minimise biases. However, the authors only provided brief details of the methods used for the review, so the validity of the data could not be assessed. For example, the criteria used to ensure the validity of the primary studies and the methods used to extract the data were not stated. In addition, the impact of differences between the primary studies was not considered.

Where evidence of effectiveness was lacking, data were derived from assumptions. Uncertainty around all outcomes was not evaluated using a sensitivity analysis. Only a sensitivity analysis on the association rate was carried out. This fact introduces uncertainty into the effectiveness results obtained. Given the limitations in the reporting of the methodology of the systematic review, it was unclear whether the best available evidence had been used to populate the model.

Validity of estimate of measure of benefit
The authors used years of life saved as the measure of health benefits. The estimation of benefits was based on the authors’ assumption that screening would avoid one death per 1,000 patients. No justification for this assumption was provided.

Validity of estimate of costs
The perspective of the analysis was not explicitly stated. Therefore, it is not possible to say whether all the categories of cost relevant to the perspective adopted were included. If considering a societal or National Health Service perspective, indirect costs should have been included in the analysis. The authors reported that the cost to society of losing a life was evaluated but, in fact, only the direct costs appear to have been included in the cost analysis. The costs and the quantities were reported separately, which enhances the generalisability of the results. The cost data were taken from actual data. No sensitivity analysis was conducted on resource use or prices. This limits the interpretation of the results. The price year was not reported, which will hamper any possible future inflation exercises. Since the costs were incurred over a lifetime horizon, discounting was appropriate. However, it was unclear whether the costs were discounted using the same discount rate as that used for the health benefits (1.5% per year).

Other issues
The authors did not compare their findings with those of other studies on the management of IBD. However, they made appropriate comparisons of their findings with those from other health care technologies, showing that screening for TPMT gene polymorphisms prior to the initiation of azathioprine therapy in the management of IBD compared favourably with other health interventions. The issue of generalisability to other settings was not directly addressed, although it was partially explored through sensitivity analyses. The authors’ conclusions reflected the scope of the analysis, and they acknowledged certain limitations of their study. For example, some data might have been exaggerated and morbidity underestimated, as they were based on small retrospective studies. In addition, some assumptions might
have overestimated the benefits of screening: screening might identify potential leucopenia patients with a better overall prognosis or patients who would have been detected by careful haematological monitoring.

**Implications of the study**
The authors suggested "most centres should offer a diagnostic service so that clinicians can utilize the test for TPMT genotype".

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None stated.

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**Other publications of related interest**

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