Screening for celiac disease in asymptomatic children with Down syndrome: cost-effectiveness of preventing lymphoma
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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 examined screening for coeliac disease (CD) in asymptomatic children with Down syndrome (DS). The serologic markers used in screening for CD included the immunoglobin A endomysial antibody and the tissue transglutaminase antibody.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of asymptomatic children with DS.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1989 and 2005. The dates to which the resource use referred were not reported. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A decision tree model was constructed to assess the costs and benefits associated with CD screening versus no screening in a hypothetical cohort of asymptomatic DS children. The time horizon of the model was lifetime. Regardless of the screening or no screening strategy, children could or could not have underlying CD and develop CD-related complications (lymphoma) or not. In the screening branch, children could have a positive or negative screen. If the screen was positive, the child underwent small bowel biopsy that confirmed or did not confirm the diagnosis of CD (biopsy was considered the ‘gold’ standard). In the case of confirmed CD, children were placed on a gluten-free diet (GFD). Thus, the costs and the number of children that developed lymphoma depended on the accuracy of the screening test: false-positives generated unnecessary costs, while true-positives led to early GFD and reduced risks of lymphoma. The structure of the decision tree was represented graphically.
Outcomes assessed in the review
The outcomes estimated from the literature were:

- the effectiveness of a GFD in preventing lymphoma;
- life expectancy in DS;
- life expectancy for persons with DS who develop lymphoma;
- the prevalence of CD in asymptomatic children with DS;
- the risk of lymphoma;
- the relative risk of lymphoma in CD;
- the sensitivity and specificity of serologic tests;
- the utility associated with a GFD; and
- the utility associated with lymphoma.

Study designs and other criteria for inclusion in the review
The authors stated that the literature was reviewed for all clinical estimates. When DS-specific data were not available, clinical estimates were derived from the general population using conservative estimates (thus biasing the analysis in favour of screening). Details of the primary studies (study samples, patient demographics and study design) were not reported. The utility weights for treated CD were obtained from a published study in which the SF-36 short form was used in Scandinavian patients. The utility of lymphoma was obtained from a Dutch study.

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
Twenty-two primary studies provided the clinical inputs.

Methods of combining primary studies
When a range of clinical values was available for a single estimate, the median value was chosen. In some circumstances the analysis was biased in favour of the screening strategy.

Investigation of differences between primary studies
Not reported.

Results of the review
The effectiveness of a GFD in preventing lymphoma was 62% (range: 51 to 100). This meant that the adherence to a GFD was estimated to be 62% and that adherence to a GFD decreased the risk of lymphoma to that of the general population.

The life expectancy in DS was 56 years (range: 52 to 60).

The life expectancy for persons with DS who develop lymphoma was 48 years (range: 38 to 58).

The prevalence of CD in asymptomatic children with DS was 3.3% (range: 1 to 6.5).

The risk of lymphoma was 0.02% (range: 0.01 to 0.047).

The relative risk of lymphoma in CD with respect to the general population was 6.3.

The sensitivity of serologic tests was 95.7% (range: 90.3 to 98.1) and the specificity was 99% (range: 94.6 to 99.8).

The utility associated with a GFD was 0.99 (range: 0.99 to 1.00).

The utility associated with lymphoma was 0.70 (range: 0.60 to 0.81).

**Measure of benefits used in the economic analysis**

Three summary benefit measures were used in the economic analysis. These were the quality-adjusted life-years (QALYs), the life-years (LYs) and the probability of preventing one case of lymphoma. All measures were calculated using a modelling approach. There was little information on the sources of the utility values. Discounting does not appear to have been performed, although it might have been relevant given the long time horizon of the analysis.

**Direct costs**

The analysis of the costs was restricted to the direct medical costs associated with screening, endoscopy and small bowel biopsy, GFD and the treatment of lymphoma. Transportation costs were not considered in order to bias the analysis in favour of screening. The costs of complications arising from endoscopy or small bowel biopsy were not included because these events are very rare. The unit costs were presented for some items but the resource quantities were not reported. The costs were derived from several sources such as Medicare or Medicaid claims, published studies and the authors’ institution. The sources of the quantities of resources used were not provided. The price year was not reported. Discounting does not appear to have been performed, although it might have been relevant given the long time horizon of the analysis.

**Statistical analysis of costs**

The costs were treated deterministically.

**Indirect Costs**

The indirect costs were not considered.

**Currency**

US dollars ($).

**Sensitivity analysis**

One- and two-way sensitivity analyses were carried out to assess the robustness of the cost-effectiveness and cost-utility ratios to variations in key clinical and economic inputs. Ranges of values were based on published data. A threshold analysis, which considered a willingness-to-pay level of $50,000 per QALY, was also performed.
Estimated benefits used in the economic analysis
The expected QALYs per patient were 55.9526 with no screening and 55.9417 with screening (difference in favour of no screening 0.0109).

The expected LYs per patient were 55.98308 with no screening and 55.98549 with screening (difference in favour of screening 0.00241).

The probability of preventing one case of lymphoma was 0.99789 with no screening and 0.99819 with screening. This resulted in 3,319 children undergoing the screening test, 137 children undergoing biopsy, and 105 children placed on a GFD for every case of lymphoma prevented.

Cost results
The cost per patient was $36.40 with no screening and $1,484.70 with screening.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios and cost-utility ratios were calculated to combine the costs and benefits of the strategies under examination.

When the costs were combined with QALYs, the incremental analysis revealed that screening was dominated by no screening, which was both more effective and less expensive.

The incremental cost per LY gained with screening over no screening was $600,864.65.

The incremental cost per one additional case of lymphoma prevented with screening in comparison with no screening was $4,806,917.22.

The results of the sensitivity analysis showed that the base-case results were robust to variations in clinical and economic inputs. Specifically, under no scenario did the cost-effectiveness of screening fall below the threshold of $50,000 per QALY. In most cases the screening strategy was dominated by no screening.

Authors' conclusions
Screening asymptomatic children with Down syndrome (DS) for coeliac disease (CD) was not cost-effective in the USA. Even in favourable scenarios, the cost per quality-adjusted life-year (QALY) far exceeded the commonly cited threshold for the definition of a cost-effective health technology.

CRD COMMENTARY - Selection of comparators
The comparator (i.e. no screening) was appropriate in that it represented the current pattern of care in the authors' context. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness analysis was based on data derived from a review of the literature, the methods and conduct of which were not described. The authors described the process that led to the choice of individual clinical estimates from among those available in the literature. However, limited information on the types of studies used as sources of data was provided. Therefore, it was not easy to assess the validity of the primary studies. In general, median values across the studies identified were chosen. The authors did not address the issue of heterogeneity in patient populations and study design across the primary studies. Sensitivity analyses on the most uncertain clinical estimates, such as published DS-specific data that were very limited, were performed. Data from the general population were used when DS-specific estimates were not available.
Validity of estimate of measure of benefit
All benefit measures were appropriate as the study aimed to assess the impact of the screening strategies on relevant dimensions of health such as (quality-adjusted) survival and cases of CD-related complications. Quality of life, in particular, represents a key aspect of the patients’ health. The utility estimates taken from published studies of Scandinavian and Dutch patients were reported. It was unclear whether these estimates are transferable to the US context, although the authors carried out sensitivity analyses to deal with this issue. Discounting was not reported although US guidelines recommend the calculation of the present value of future benefits.

Validity of estimate of costs
The perspective of the economic analysis did not reflect the viewpoint of society since, as the authors stated, productivity losses and transportation costs were not considered. It was noted that the exclusion of these costs should have favoured the screening strategy. The authors clearly explained the estimation of the costs and provided details on the selection of cost estimates from the available sources. When the costs were derived from other countries and from different periods, appropriate currency conversions were carried out and the effect of inflation was considered. Owing to the variability across sites, extensive sensitivity analyses were carried out on the cost estimates. Discounting was not performed, although it was relevant given the long time horizon of the model. The price year was not reported, which could hinder any reflation exercises in other time periods.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies. Further, the issue of the generalisability of the study results to other settings was not explicitly addressed, although the use of sensitivity analysis will have enhanced, to some extent, the external validity of the study. In general, the authors stated that clinical and economic inputs were selected in order to bias the model towards screening. For example, the potential costs associated with complications or the rate of death associated with endoscopy (these costs and risk were incurred only in the screening branch) were not taken into consideration. A limitation of the analysis was the fact that morbidities were not considered. Thus, if one assumes that treatment of asymptomatic CD decreases other medical costs, then the analysis might have underestimated the benefits of screening. However, due to the wide cost-differences, the inclusion of morbidities in the model should not substantially alter the conclusions of the analysis. The authors highlighted the difficulties in eliciting estimates of quality of life in children with DS.

Implications of the study
The study results do not support routine screening for CD in DS children. However, the authors stated that families should be given information about the risk of CD in order to allow an evaluation of the costs and benefits of managing a DS child with CD.

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Other publications of related interest
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**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Celiac Disease /complications /diagnosis /economics /epidemiology; Child; Comorbidity; Cost-Benefit Analysis; Costs and Cost Analysis; Decision Trees; Disease Susceptibility; Down Syndrome /complications; Gastrointestinal Neoplasms /economics /epidemiology /etiology /prevention & control; Humans; Insurance, Health, Reimbursement /economics /statistics & numerical data; Lymphoma, Non-Hodgkin /economics /epidemiology /etiology /prevention & control; Mass Screening /economics; Medicaid /economics /statistics & numerical data; Medicare /economics /statistics & numerical data; Models, Theoretical; Prevalence; Quality-Adjusted Life Years; Risk; Sensitivity and Specificity

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