Screening for Wilms tumor and hepatoblastoma in children with Beckwith-Wiedemann syndromes: a cost-effective model

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
Screening for Wilms tumour (WT) and hepatoblastoma in children with Beckwith-Wiedemann syndrome (BWS) was compared with no screening. The strategies compared were ultrasound screening every 4 months from birth and no screening. Positive results of the ultrasound screening were confirmed by computed tomography (CT).

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The effects of screening until 7 years of age were evaluated in two hypothetical cohorts of children with BWS, from birth until different ages (up to 10 years).

Setting
Although not stated, the setting appears to have been secondary or tertiary care, as BWS is a rare syndrome followed by specialists.

Dates to which data relate
The effectiveness data were obtained from studies published from 1975 to 1999. The resource use data were derived using authors’ assumptions and data published in 1995. The price year was 2000.

Source of effectiveness data
The estimates of effectiveness were derived from a review of published studies and authors’ assumptions.

Modelling
A spreadsheet model was used to analyse two hypothetical cohorts of 1,000 children with BWS, one undergoing screening and one not undergoing screening. The cost-effectiveness of screening was determined by comparing the costs of screening, diagnostic follow-up and treatment, and by comparing the predicted life expectancy of the respective cohorts. Predicted life expectancy and cancer treatment costs were modelled as a function of cancer stage at diagnosis (as well as favourable/non favourable histology for WT) and stage-specific survival estimates. Although not stated, the model appears to have been a state transition model.

Outcomes assessed in the review
Inputs to the model were:

the age-specific incidence of WT and hepatoblastoma, and their stage distributions and survival rates;

histological type in the case of WT;

the frequency of ultrasound screening;

mortality from other causes; and

the sensitivity and specificity of ultrasonography.

**Study designs and other criteria for inclusion in the review**
The authors did not report the criteria for inclusion in the review, which was probably a narrative review. Data from a national registry of BWS, a national WT study and a large case series of hepatoblastoma were used to calculate incidence and mortality.

**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**
The effectiveness inputs were derived from 10 studies and data from a personal communication.

**Methods of combining primary studies**
The primary studies were combined in a narrative.

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

**Results of the review**
Age-specific incidences of WT and hepatoblastoma were reported for each of the first 10 years of life. These ranged from 2.01% (year 1) to 0.16% (year 10) for WT, and from 1.98% (year 1) to 0% (year 10) for hepatoblastoma.

The stage distributions for unscreened and screened patients with WT and with hepatoblastoma were also presented.

The sensitivity of ultrasonography came from one study and was 100%.

**Methods used to derive estimates of effectiveness**
The methods used to derive estimates based on assumptions were not reported.
Estimates of effectiveness and key assumptions
The principal assumptions reported by the authors were:

- Screening was conducted from birth until 7 years of age;
- Ultrasonography was 95% specific for the detection of a stage I or III WT of at least 3 cm in diameter and a clinical stage I hepatoblastoma;
- Screening would result in one downward stage shift of WT and hepatoblastoma when compared with no detection; and
- The frequency of ultrasound screening in the base-case was every 4 months.

Measure of benefits used in the economic analysis
The measure of benefits used was the life-years gained (LYG).

Direct costs
Both the costs and benefits were discounted at a 3% rate in the base-case scenario. The items included were abdominal sonography, cost of a false-positive result (evaluated by CT), and the costs of cancer treatment. The treatment costs for hepatoblastoma were not included, as they were considered to be equal for early and later stages. The treatment costs for early versus late WT considered only radiotherapy, as it was the main difference in treatment. The quantity/cost boundary was not stated. The estimation of the quantities, and thus the costs, was derived using modelling. The costs were derived from a large health maintenance organisation and published sources. The costs were reflated, when appropriate, to US dollars (2000) using the medical care component of the consumer price index. The incremental cost of radiotherapy in WT was derived using cost-to-charge adjustments. The resource and cost data related to dates ranging from 1993 to 1995.

Statistical analysis of costs
A statistical analysis of the costs was not conducted. The cost data were handled deterministically.

Indirect Costs
The authors used data from a willingness to pay questionnaire study to calculate the indirect cost of the cancer screening programme, that is, the cost associated with time and opportunity lost by the family. A questionnaire was mailed to 200 parents of patients in the BWS registry, and 62% responded. The question asked was how much would they be willing to pay for a new test, as good as ultrasound, but that required only a Polaroid picture taken at home. The average response was 42 US dollars (in 1993). This was reflated to the year 2000 and used to calculate the total screening costs.

Currency
US dollars ($).

Sensitivity analysis
One-way sensitivity analyses were conducted on test operating characteristics, sonogram costs, the detection of WT only but not hepatoblastoma, treatment costs, cost of a false positive, and discount rates. A worst-case scenario was also conducted to evaluate several unfavourable assumptions simultaneously. The authors selected the ranges to be investigated.

Estimated benefits used in the economic analysis
The total discounted life-years saved in a cohort of 1,000 children if screening was stopped at years 1 to 10 were:
117.91 year 1), 185.62 (year 2), 218.6 (year 3), 232.74 (year 4), 241.45 (year 5), 245.72 (year 7), 247.18 (year 8), 247.82 (year 9) and 248.44 (year 10).

Cost results
The total discounted costs in a cohort of 1,000 children if screening was stopped at years 1 to 10 were:

$656,045 (year 1), $1,226,806 (year 2), $1,760,685 (year 3), $2,265,579 (year 4), $2,745,898 (year 5), $3,205,460 (year 6), 3,647,889 (year 7), $4,047,686 (year 8), $4,486,755 (year 9) and $4,885,239 (year 10).

Synthesis of costs and benefits
The average cost per LYG and the incremental cost per LYG were calculated for each strategy.

In the base-case analysis, screening for children with BWS up to 7 years cost $14,740 per LYG. This average cost increased if screening was advanced from 7 to 8 ($16,377), 9 ($17,996) or 10 years ($19,561). It decreased to $5,503 if screening was stopped in the first year.

The incremental cost per LYG was much higher than the average result, because most of the benefits were accrued during the first years of screening. Screening up to age 4 resulted in an acceptable range (less than $50,000/LYG), while the incremental cost-effectiveness ratios of extending screening from age 5 to age 10 ranged from $54,884/LYG to $647,164/LYG.

When variables such as the cost of screening, discount rate and screening effectiveness were varied based on high and low estimates, the incremental cost per LYG remained less than $50,000 for screening until age 4. In the worst-case scenario (discount rate 7%, false-positive rate 10%, false-positive costs $1,320, and a 50% reduction in stage shift) the average cost per LYG of the base-case increased to $95,294. The incremental cost per LYG when screening was increased from 7 to 8 years was $1,894,165. Under this scenario, screening would have to stop at 3 years for the incremental costs to remain below $100,000/LYG.

Authors' conclusions
Under the model's assumptions, abdominal sonography examination in children with Beckwith-Wiedemann syndrome (BWS) is a reasonable strategy for a cancer screening programme. A cancer screening trial is warranted to determine if, when and how often children with BWS should be screened, and to determine the cost-effectiveness in clinical practice.

CRD COMMENTARY - Selection of comparators
The authors stated there is controversy about screening children with BWS and the recommended screening frequency. Abdominal ultrasonography seems to be the currently used test for screening and, although no explicit justification was given for the comparator of no screening, it appears to have represented a possible alternative in the authors' setting. You should consider if this is relevant to your own setting.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature was carried out. They may have used the data from the available studies selectively. However, as the model concerned a rare disease, they probably used the best available data (national registries) for the epidemiological inputs to their model. The estimate of effectiveness was derived credibly from the primary studies. The assumptions made by the authors were usually justified with reference to the medical literature. The main exception was the benefit of screening, which was assumed to provide a one-stage shift in diagnosis. Although this assumption was not evaluated in a one-way sensitivity analysis, it was included for the worst-case scenario analysis. The specificity of ultrasound was also estimated. The ranges used in the sensitivity analysis usually involved doubling or halving the baseline estimate.
Validity of estimate of measure of benefit
The estimation of benefits (LYG) was determined from the decision analytic model, which seems to have been an appropriate framework in which to evaluate the alternative strategies.

Validity of estimate of costs
The authors did not report the perspective used, but as they included indirect costs it is likely that they intended it to be societal. The costs included were for the sonograph, CT, incremental advanced stage treatment for WT, and the indirect costs. Other relevant costs, such as the treatment of hepatoblastoma or low-stage WT, were not included in the base-case since they were assumed to be common between the strategies. You should judge whether these cost categories are appropriate in your own setting. Other costs excluded were those for the physician's visit to inform the test results, which could have the effect of making the screening look less cost-effective. Also excluded were the late effects of radiation therapy, such as scoliosis, secondary malignancy and congestive heart failure.

The unit costs were reported. Resource use was calculated using the model and was not reported separately. A sensitivity analysis of quantities was conducted for the worst-case scenario only. It would have been useful had the authors evaluated the impact in a one-way sensitivity analysis for each quantity of interest. The unit costs were derived from a personal communication, published literature, a questionnaire to the parents and authors' opinions. Sensitivity analyses were also conducted on the unit cost of sonography and for the inclusion of hepatoblastoma costs. The date to which the prices related was reported, which would help those undertaking reflation exercises.

Other issues
The authors stated that, based on earlier work showing screening effectiveness, they had demonstrated its potential cost-effectiveness and it could help policy making in other rare genetic predisposition syndromes. The authors also compared their results with other cancer screening programmes. The issue of generalisability to other settings was not specifically addressed, although the sensitivity analyses conducted help in this regard. The authors reported further limitations. For example, the influence of lead time and length time bias, the optimistic assumption that the sensitivity of sonography is 100%, and the fact that its cost was not empirically derived.

Implications of the study
The authors stated that the incremental analysis suggests that screening children with BWS appears to have been cost-effective, and that stopping screening at age 4 would be the most cost-effective approach since the incidence after that age is very low. From the age of 4 to 7 or 8, screening looks potentially cost-effective.

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