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
Endoscopic screening for pancreatic cancer (PC) in familial PC kindreds, using endoscopic ultrasonography (EUS), was examined. The screening protocol used EUS in combination with endoscopic retrograde cholangiopancreatography (ERCP). Abnormal screening results were used to select patients with dysplasia for preventive total pancreatectomy.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients who were 50 years old and members of familial PC kindreds. Only patients who would consider a pancreatectomy in response to abnormal screening results were considered.

Setting
The setting was a hospital. The economic study was carried in the USA.

Dates to which data relate

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' assumptions.

Modelling
A decision tree model was constructed to assess the clinical and economic impact of PC screening versus no screening in a hypothetical cohort of 100 patients. In the screening branch, patients underwent EUS. Those with negative results underwent no further testing. Patients with an abnormal EUS result underwent ERCP for confirmation. An abnormal EUS result was defined by the clear presence of at least two of the following abnormalities: heterogeneous parenchyma with echogenic foci, hypoechoic nodules, hyperechoic main duct walls, or discrete masses. Those with an abnormal ERCP result were referred for total pancreatectomy, which could result in substantial morbidity and mortality. An abnormal ERCP result was defined by the presence of main duct strictures, focal side branch duct irregularity or ectasia, small sacculations, and/or grape-like clusters of saccules. Complications of diagnostic ERCP (pancreatitis) were also considered, but gastrointestinal bleeding and perforation were not modelled. Undetected PC could develop at any stage of the model. In the no-screening branch, individuals had similar pre-test probabilities of dysplasia. The time
horizon of the model was lifetime.

**Outcomes assessed in the review**
The outcomes estimated from the literature were:

- the prevalence of dysplasia;
- the probability that EUS will be abnormal;
- the probability of progression to PC given that dysplasia is present;
- the probability that ERCP will be abnormal given abnormal EUS;
- the probability of complications with ERCP (pancreatitis);
- the operative mortality with total pancreatectomy;
- the life expectancy of a 50-year-old individual;
- the time for progression from dysplasia to PC;
- the median time from the development of PC until death; and

the life expectancy of a newly diagnosed 50-year-old diabetic patient (proxy for life expectancy of a survivor of total pancreatectomy).

**Study designs and other criteria for inclusion in the review**
It was not stated whether a systematic review of the literature had been undertaken to identify relevant studies. No information on the design and characteristics of the primary sources was provided. The authors stated that most of the clinical data came from the database of their Familial Pancreatic Cancer Screening Program. Life expectancy was derived from US statistics.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
Not stated.

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

**Number of primary studies included**
Thirteen studies provided the evidence.

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

**Investigation of differences between primary studies**
Results of the review
The prevalence of dysplasia was 0.20 (range: 0.01 - 0.50).

The probability that EUS will be abnormal was 0.34 (range: 0.10 - 0.75).

The probability of progression to PC given that dysplasia is present was 0.90 (range: 0.75 - 1.00).

The probability that ERCP will be abnormal given abnormal EUS was 0.45 (range: 0.05 - 0.75).

The probability of complications with ERCP was 0.051 (range: 0.003 - 0.082).

The operative mortality with total pancreatectomy was 0.03 (range: 0.01 - 0.05).

The life expectancy with total pancreatectomy was 29.7 years (range: 14.5 - 29.7).

The time for progression from dysplasia to PC was 10 years, and the median time from the development of PC until death was 0.8 years. Therefore, the time from the development of pancreatic dysplasia until death was 10.8 years (range: 3.8 - 10.8).

The life expectancy after total pancreatectomy was 19.1 years (range: 5 - 20).

Methods used to derive estimates of effectiveness
Authors' estimates were used to derive clinical data when probabilities were not available from the literature.

Estimates of effectiveness and key assumptions
EUS and ERCP both had a sensitivity of 0.90 (range: 0.50 - 1). The probability of developing PC in the absence of dysplasia was 0.01 (range: 0 - 0.20).

Measure of benefits used in the economic analysis
The summary benefit measure was the expected survival. This was estimated using the modelling approach. Life-years gained were discounted at an annual rate of 3%.

Direct costs
Discounting was relevant because of the long time horizon of the study. An annual discount rate of 3% was applied. The unit costs were presented separately from the quantities of resources used for most cost items. The health services included in the economic evaluation were EUS, ERCP, treatment of ERCP-related pancreatitis, pancreatectomy, the lifetime costs after total pancreatectomy, and management of PC care. The costs associated with the treatment of ERCP-related pancreatitis included hospitalisation for varying degrees of pancreatitis severity. The cost/resource boundary of the third-party payer was adopted. Resource use data came from authors' assumptions on the frequency of diagnostic tests and published evidence. The costs came from Medicare reimbursement rates and published studies. The lifetime costs after total pancreatectomy were estimated using the lifetime costs of management of diabetes care. The costs were presented as 2000 values using the annual Consumer Price Index for medical care.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were included in a secondary analysis where a societal perspective was adopted. The indirect costs of PC care were derived from a published study, but no details were provided.

Currency
US dollars ($).

Sensitivity analysis
Univariate sensitivity analyses were carried out on all model inputs, to examine the impact of variations in base-case estimates on the incremental cost-effectiveness ratios (ICERs). Published and estimated ranges of values were used. Threshold analyses for equivalent outcomes for the two strategies were also performed. Tornado diagrams were constructed to identify the variables with the greatest influence on the model, and two-way sensitivity analyses were also performed for specific combinations of variables.

Estimated benefits used in the economic analysis
In the cohort of 100 patients, the discounted survival was 1,758 life-years with screening and 1,720 life-years with no screening. Thus, screening for PC led to a gain of 38 life-years.

Cost results
In the cohort of 100 patients, the discounted direct costs were $968,733 ($2,623,735 including indirect costs) with screening and $327,118 ($4,037,663 including indirect costs) with no screening.

Screening for PC cost an additional $641,615 when only the direct costs were considered, but saved $1,413,928 when the indirect costs were also included.

Synthesis of costs and benefits
The costs and benefits were combined using an incremental analysis and ICERs were calculated.

The incremental cost per life-year saved with screening over no screening was $16,885 from the perspective of the third-party payer. From a societal perspective, PC screening dominated no screening, which was both less effective and more costly.

The expected survival advantage of screening was sensitive to the prevalence of dysplasia (threshold value less than 16%), sensitivities of EUS and ERCP (threshold values less than 84% and 68%, respectively), and life expectancy (threshold values: 27 years, or time between onset of dysplasia and death greater than 12 years).

The ICER from the third-party payer perspective was sensitive to the same variables as was the expected survival. The ICERs estimated from the societal perspective were robust to variations in base-case assumptions, and screening dominated no screening in all scenarios. Similar conclusions were reached in the two-way sensitivity analysis, where the ICER was generally below the value of $25,000 per life-year saved from the perspective of the third-party payer, and screening dominated no screening from the perspective of society.

Authors' conclusions
The screening of high-risk members of familial pancreatic cancer (PC) kindreds was a cost-effective strategy from the perspective of the third-party payer, with an incremental cost-effectiveness ratio (ICER) well within the range of other commonly accepted cancer screening strategies. Screening was cost-saving from the perspective of society, owing to the substantial impact of the indirect costs. The analysis suggested that for screening to be particularly cost-effective, patients should be carefully selected and should also have a normal life expectancy.
CRD COMMENTARY - Selection of comparators
The authors provided a justification for their choice of the comparator. No screening was selected because there were currently no clinically useful alternatives for the detection of early-stage PC. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published data and authors' assumptions. It was unclear whether a systematic review of the literature had been undertaken to identify relevant studies. No information on the primary studies was provided. Therefore, it is not possible to examine the validity of the primary studies. Also, the two most important parameters (sensitivity of EUS and ERCP) were based on expert opinion. However, the authors took the issue of uncertainty in all clinical inputs into consideration and performed extensive sensitivity analyses.

Validity of estimate of measure of benefit
Survival was an appropriate benefit measure, not only because it captures the most relevant aspect of the impact of screening on patients' health, but also because it is a measure comparable with the benefits of other health care interventions. Discounting was applied, as recommended in the USA, and the use of alternative rates was investigated in the sensitivity analysis. The authors noted that utility values were not available, thus they could not estimate quality-adjusted life-years.

Validity of estimate of costs
The authors adopted two different prospective in the analysis of costs, which was useful since policy decision makers might be more interested in the comparison of direct costs rather than in a broader perspective. Indeed, the direct costs are the only ones borne by the health care system. The unit costs and the quantities of resources used were given separately only for some categories of costs, because aggregated cost data were presented for those items that were estimated from published studies. The source of the data was reported. The price year was also reported, which aids reflation exercises in other settings. However, no details of the indirect costs were provided. The costs were treated deterministically, but the economic estimates were varied in the sensitivity analysis to examine the robustness of the results of the study to variations in the cost estimates.

Other issues
The authors did not compare their findings with those from other studies. They also did not address the issue of the generalisability of the study results to other settings. However, extensive sensitivity analyses were carried out, which enhances the external validity of the study. The study referred to patients at high-risk of PC and this was reflected in the authors' conclusions.

Implications of the study
The study results supported the use of screening for PC in high-risk individuals. Endoscopic screening was not recommended in individuals with chronic pancreatitis and in those who ingest excessive amounts of alcohol. Further, testing should be restricted to centres with particular experience in pancreatic disorders.

The authors suggested that further research should be carried out to investigate the accuracy of EUS and ERCP. In general, the authors pointed out that future studies should verify the assumptions made in the decision model. Future studies should identify biomarkers that would allow a more precise risk stratification, such that screening could be applied only to individuals at high risk.

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Other publications of related interest


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