Lifetime effects, costs, and cost effectiveness of testing for human papillomavirus to manage low grade cytological abnormalities: results of the NHS pilot studies

Legood R, Gray A, Wolstenholme J, Moss S

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 health interventions examined in the study were five strategies for the management of low-grade cytological abnormalities in women undergoing cervical smear, namely:

Strategy A: Liquid based cytology only.

Strategy B: Combined liquid based cytology and human papillomavirus (HPV) testing for women with borderline or mildly dyskaryotic results; women who tested positive for the virus were referred for immediate colposcopy and women who tested negative were recalled at six months for repeat cytology and HPV testing.

Strategy C: Same as strategy B except that women aged under 35 who initially tested positive were not referred for colposcopy; even if repeat tests for these women gave negative results, they were recalled for a third combined test at 12 months.

Strategy D: Combined liquid based cytology and adjunctive HPV testing (as described in strategy B) for women aged 35 or over, and liquid based cytology only for women under 35 (as described in strategy A).

Strategy E: Combined liquid based cytology and adjunctive HPV testing (as described in strategy B) but no testing for HPV in repeat tests.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population referred to a hypothetical cohort of women aged 25-64 with borderline or mildly dyskaryotic cervical smear results.

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

Dates to which data relate
Effectiveness data were derived from studies published between 1980 and 2005. No dates were explicitly reported for resource use data. The costs used referred to 2001/2002 prices.

Source of effectiveness data
The effectiveness evidence came from a synthesis of published studies and authors’ assumptions.

**Modelling**
A previously published natural history model was used in order to assess the long-term effects, costs, and cost-effectiveness of the 6 strategies for the diagnostic management of women with borderline or mildly dyskaryotic cervical smear results. This was a Markov model but limited details were provided. The following health states were considered: healthy, HPV only, cervical intraepithelial neoplasia (CIN) grade 1, CIN-2, or CIN-3, and invasive cancer stages I-IV. The time horizon of the model was lifetime. The cycle length was six months. In all strategies, women with moderate or severe cytology results were referred directly for colposcopy; inadequate cytology results were retested immediately; and women with normal results returned to routine screening. When only cytology was used for repeat testing every six months (strategies A and E and women aged less than 35 in strategy D), women were referred for colposcopy after three borderline or two mildly dyskaryotic smear results. Women only returned to routine screening after three consecutive negative results, again at six-month intervals.

**Outcomes assessed in the review**
The outcomes estimated from the literature were attendance rates, transition probabilities, incidence rates of pre-invasive disease, sensitivity and specificity of HPV testing, effectiveness of colposcopy, and probabilities of survival after a diagnosis of invasive cancer.

**Study designs and other criteria for inclusion in the review**
It was unclear whether clinical evidence was derived from a systematic review of the literature. Limited information on the design and other features of the primary studies was provided. Sensitivity and specificity of HPV testing were taken from a meta-analysis. Survival from invasive cancer and mortality due to other causes were taken from UK life tables.

**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 reported.

**Number of primary studies included**
Nine studies were used as the source of evidence.

**Methods of combining primary studies**
Primary estimates were not combined as each study provided a set of estimates.

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

**Results of the review**
The following attendance rates were estimated: 81% (range: 76% - 85%) for routine smear, 79% (range: 77% - 80%) for repeat smear (age <35); 85% (range: 84% - 87%) for repeat smear (age >/= 35), 95% (range: 97% - 93%) for
colposcopy (age <35), and 93% (range: 90% - 96%) for colposcopy (age >/=35).

The prevalence of HPV infection at age 15 was 0.1, while the prevalence of CIN-1 at age 15 was 0.01.

The age-specific incidence of HPV infection was 0.051-0.089 for ages 15 to 19 years, 0.078-0.051 for ages 20 to 23 years, 0.025 for ages 24 to 29 years, 0.005 for ages 30 to 49 years, and 0.003 for ages >/= 50 years.

The age-specific regression rates of HPV infection were 0.33 (range: 0.26 - 0.54) for ages 15 to 24, 0.21 (range: 0.18 - 0.26) for ages 25 to 29, 0.05 (range: 0.03 - 0.07) for ages >/= 30.

The progression rate from HPV to CIN-1 was 0.04 (range: 0.03 - 0.06).

The proportion of HPV infections progressing to CIN-2 or CIN-3 was 0.1 (range: 0.05 - 0.5).

The regression rate from CIN-1 to HPV or healthy was 0.084 (range: 0.074 - 0.126) for ages 15 to 34 and 0.042 (range: 0.029 - 0.074) for ages >/= 35.

The proportion of CIN-1 reverting to healthy was 0.9 (range: 0.5 - 1.0).

The progression rate from CIN-1 to CIN-2 or CIN-3 was 0.0087 (range: 0.0087 - 0.029) for ages 15 to 34 and 0.035 (range: 0.029 - 0.056) for ages >/= 35.

The regression rate from CIN2/3 to CIN1 or healthy was 0.035 (range: 0.0292 - 0.056).

The proportion of CIN2/3 reverting to healthy was 0.5 (range: 0.0 - 0.5).

The progression rate from CIN2/3 to invasive cancer was 0.025 (range: 0.018 - 0.034).

The sensitivity and specificity of HPV testing were, respectively, 0.948 (range: 0.927 - 0.969) and 0.673 (range: 0.582 - 0.764).

The effectiveness of colposcopy was 90% (range: 80% - 100%).

The progression rate from stage I to stage II was 0.13.

The probability of symptoms in stage I was 0.08.

The progression rate from stage II to stage III was 0.23.

The probability of symptoms in stage II was 0.12.

The progression rate from stage III to stage IV was 0.44.

The probability of symptoms in stage III was 0.37.

The probability of symptoms in stage IV was 0.68.

The annual probability of survival after invasive cancer diagnosis was 0.97-0.99 for stage I, 0.77-0.96 for stage II, 0.54-0.90 for stage III, and 0.49-0.88 for stage IV.

Methods used to derive estimates of effectiveness
The authors made some assumptions that were used in the decision model.

Estimates of effectiveness and key assumptions
For all strategies, 90% of cases of invasive cancer were detected at each screening round. All coloscopies were
assumed to be 100% sensitive and specific, and all abnormalities when found at colposcopy were treated.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the number of life-years (LYs) that were estimated using the decision model. A 3.5% annual discount rate was applied in the first 30 years and 3% thereafter.

**Direct costs**
The analysis of costs took the perspective of the NHS and included the following direct medical costs: conventional cytology, liquid based cytology, HPV test, colposcopy (for patients with and without CIN), and cancer care costs. Costs of diagnostic tests included equipment, consumables, and staff. Unit costs were presented for most items but costs of cancer care were given as macro-categories and were stage-dependent. Limited information on resource consumption was provided. Costs of cancer care were estimated from a previous UK study. Other costs came from market prices and typical NHS sources. Resource consumption was mainly derived from the 3 NHS pilot sites. Discounting was relevant as lifetime costs were estimated, and a 3.5% annual discount rate was applied in the first 30 years and a 3% thereafter. Costs were inflated to 2001/2002 values using the NHS Health and Community Price Index.

**Statistical analysis of costs**
Costs were treated deterministically in the base case but probabilistic distributions were assigned in the sensitivity analysis.

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

**Currency**
UK pounds sterling (£). Some costs were also reported in Euros (EUR) and US dollars ($) but exchange rates were not given.

**Sensitivity analysis**
Univariate sensitivity analyses were carried out to assess the impact of individual model inputs on total cost-effectiveness ratios. Alternative values tested in the analysis were derived from the literature. A probabilistic sensitivity analysis was also performed and all model inputs were assigned a probabilistic distribution. Beta distributions were mainly used for probabilities of events, while gamma distributions were applied to economic data. The results of the stochastic simulation were presented using a cost-effectiveness acceptability curve, which showed the optimal strategy at different values the service payer would be willing to pay for a gain in life years.

**Estimated benefits used in the economic analysis**
In comparison with conventional cytology, the LYs gained were 0.0019 with strategy A, 0.0034 with strategy D, 0.0039 with strategy C, 0.0049 with strategy E, and 0.0050 with strategy B.

The lifetime risk of death from invasive cancer was also reported and was 0.0049 with strategy A, 0.0045 with strategy B, 0.0046 with strategies C and D, and 0.0045 with strategy E.

**Cost results**
In comparison with conventional cytology, the extra costs were 9.9 with strategy A, 12.7 with strategy D, 20.2 with strategy C, 19.1 with strategy E, and 19.9 with strategy B. The numbers of smears, HPV tests, colposcopies, and treatments for invasive cancers were also reported.
Synthesis of costs and benefits
Incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative diagnostic strategies. After excluding extended dominated strategies, the incremental cost per LY gained was 3,735 with strategy D, 4,233 with strategy E, and 18,605 with strategy B.

The univariate sensitivity analysis showed that the ranking of the strategies did not change when model inputs were varied. Cost parameters had a great impact on total costs, as expected. Strategy A became the dominant strategy when the minimum value for the cost of liquid-based cytology was considered. When the sensitivity of cytology increased, the effectiveness of HPV testing decreased: particularly for surveillance of women with initial negative results for HPV.

The probabilistic sensitivity analysis showed that there was considerable uncertainty in both the incremental costs and incremental gains associated with all strategies. If the health service payer was willing to pay between 7,500 (EUR 11,100; $13,000) and 30,000 per LY gained, strategies in which HPV testing was added to liquid based cytology screening to prioritise all women with borderline or mild dyskaryotic smear results for immediate colposcopy gave the greatest net health benefit.

Authors' conclusions
The authors concluded that testing for HPV in women with low grade cytological abnormalities was likely to be cost-effective under current UK screening protocols. The analysis suggested that the most cost-effective strategies were those that used HPV testing to triage all women with an initial borderline and mild smear result, using cytology to follow-up women only with a negative test result for HPV.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate given that a large range of possible diagnostic strategies was considered in the analysis. All strategies were evaluated within the current UK screening protocol. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published studies and authors' opinions. However, it is unclear whether a systematic review of the literature was performed. In effect, primary studies appear to have been identified selectively. The sources searched to identify primary studies were not extensively reported and no information on the characteristics of these studies was provided. Thus, it is not possible to assess the robustness of the primary estimates. Some evidence came from a pilot study that was carried out in the UK and the details of which had been published elsewhere. Some assumptions were also made. Extensive sensitivity analyses were performed to address the issue of uncertainty in all clinical inputs. Typical distributions for probabilities of events were used in the probabilistic analysis.

Validity of estimate of measure of benefit
The use of LYS as the summary benefit measure is appropriate because expected survival represents a relevant dimension of health for patients with cervical cancer. The impact of the interventions on quality of life was not investigated, but studies on HPV usually focus on survival. The impact of using alternative discount rates was investigated in the sensitivity analysis. An advantage of LYS is that they can be compared with the benefits of other health care interventions.

Validity of estimate of costs
The analysis of costs reflected the perspective chosen for the analysis. A breakdown of cost items was not provided for all costs since some costs were presented as macro-categories; this, however, is quite typical in the assessment of costs for cancer care. The source of unit costs was reported. Resource consumption was mainly derived from the experience of NHS pilot hospitals, which should reflect actual patterns of care in the UK. Costs were treated deterministically in the base case but a probabilistic approach was used in the sensitivity analysis for all economic inputs. Typical distributions for economic parameters were used. Furthermore, the uncertainty around cost estimates was investigated.
in the univariate analysis. The price year was provided, which facilitates relflation exercises in other time periods.

**Other issues**
The authors stated that their findings were comparable with those observed in a UK study as well as in a US study, although details of these economic evaluations were not provided. The issue of the generalisability of study results to other settings was implicitly addressed in the sensitivity analysis, in which all model inputs were varied within reasonable ranges. This enhances the external validity of the study. The authors noted that the validity of the study was limited by the lack of data on both quality of life implications and societal costs. The results of the base case analysis and those resulting from the sensitivity analysis were clearly presented (although the latter findings were only reported in the web appendix).

**Implications of the study**
The study results appear to support strategies that use HPV testing to manage women with an initial borderline and mild smear result, with cytology being limited to following-up only those women with a negative test result for HPV. The authors note that future studies should investigate aspects related to quality of life and time that women spend to attend surveillance.

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**Other publications of related interest**


**Indexing Status**
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**MeSH**
Adult; Cervical Intraepithelial Neoplasia /economics /prevention & control /virology; Costs and Cost Analysis; Cytological Techniques /economics /methods; Female; Humans; Mass Screening /economics /standards /utilization; Middle Aged; Papillomaviridae; Patient Acceptance of Health Care /statistics & numerical data; Pilot Projects; Sensitivity and Specificity; State Medicine /economics; Tumor Virus Infections /economics /prevention & control; Uterine Cervical Neoplasms /economics /prevention & control /virology; Vaginal Smears /economics /statistics & numerical data