Prediction of cervical intraepithelial neoplasia grade 2-3 using risk assessment and human papillomavirus testing in women with atypia on Papanicolaou smears

Shlay J C, Dunn T, Byers T, Baron A E, Douglas J M

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 intervention examined in the study was human papillomavirus (HPV) DNA testing to designate risk status aimed at diagnosing cervical intraepithelial neoplasia (CIN) 2-3 on biopsies in women with atypia on Papanicolaou smears.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women older than 12 years of age, not pregnant or menstruating, with a single atypical Papanicolaou smear diagnosis where atypia was defined as either atypical squamous cells of undetermined significance (ASCUS), ASCUS favour dysplasia, ASCUS favour reactive, or atypical glandular cells of undetermined significance (AGCUS).

Setting
The setting of the study was an urban public hospital. The economic study was conducted at the Women's Care Clinic at Denver Health, Denver, Colorado, USA.

Dates to which data relate
Effectiveness evidence and data on resource use were gathered from September 1997 to April 1999. The price year was 1999.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were performed and it was determined that a sample of 195 women would result in 80% power to detect a minimum odds ratio (OR) of 5.2 at the 0.05 level of significance for the association between high-risk HPV and CIN 2-3. Patient selection was based on those women referred to the study hospital for a single atypical
Papanicolaou smear between September 1997 and April 1999. A sample of 195 patients was recruited (mean age: 33 years, range: 15 - 76 years; 57% Hispanic, 21% white, 16% black, and 6% other ethnicities).

**Study design**
The study was based on the analysis of a prospective cohort of patient, without an explicit comparison group. All patients referred to the hospital underwent a visit after a median of 64 days (range: 12 - 430 days) after the atypical Papanicolaou smear. Patients completed a questionnaire, underwent colposcopic examination, and finally a biopsy was performed for those areas which appeared abnormal on colposcopy. Length of follow-up was 6 months. The study was carried out in a single centre (the Women's Care Clinic at Denver Health in Denver). Assessment of the outcome was blind, since laboratory personnel were blinded to results of the questionnaire and biopsy results.

**Analysis of effectiveness**
All patients included in the study were accounted for in the analysis. The primary health outcomes used in the effectiveness analysis were the number of women HPV-positive, the high- and low-risk types, CIN 2-3 prevalence, sensitivity, specificity, and positive and negative predictive values of the HPV testing, the OR associating CIN 2-3 and low- and high-risk types. Specimens were considered positive for high or low risk types if Hybrid Capture II microplate assays (Digene Corporation, Silver Springs, MD, USA) chaemoluminescence was at or above 1.0 pg/mL. Individuals with either high-risk HPV or high- and low-risk HPV were designated as having high-risk HPV. The OR was adjusted for confounders such as parity, recent douching, current smoking, age, etc.

**Effectiveness results**
The effectiveness results were as follows:

The number of women HPV-positive was 73 (37.4%), 46 (23.6%) were a high-risk type, 15 (7.7%) were high- and low-risk types, and 12 (6.2%) were low-risk type.

High-risk HPV infection rate was 48.7% in women aged under 30 years and 28.6% in those aged 30 years or over, (p<0.001).

CIN 2-3 prevalence was 15 cases (7.7%) and no cervical cancer was detected, 14 cases being associated with high-risk HPV.

For CIN 2-3 adjusted OR was 110.08, (95% CI: 8.35 - 999.00).

HPV testing resulted in 31.3% of patients being referred for colposcopy.

Sensitivity, specificity, positive and negative predictive values were:

- sensitivity 93.3% (95% CI: 89.8% - 96.8%), specificity 73.9% (95% CI: 67.7% - 80.1%), positive predictive value 23% (95% CI: 17.1% - 28.9%), and negative predictive value 99.3% (95% CI: 98.1% - 100%).

In the subgroup of patients younger than 30 years of age, sensitivity, specificity, positive and negative predictive values were as follows:

- sensitivity 100% (95% CI: 94.0% - 100%), specificity 57.4% (95% CI: 46.4% - 68.4%), positive predictive value 21.6% (95% CI: 12.3% - 30.9%), and negative predictive value 100% (95% CI: 94.0% - 100%).

In the subgroup of patients of aged 30 years or over, sensitivity, specificity, positive and negative predictive values were:

- sensitivity 85.7% (95% CI: 74.9% - 92.0%), specificity 83.9% (95% CI: 77.3% - 90.5%), positive predictive value 25.0% (95% CI: 17.2% - 32.8%), and negative predictive value 98.9% (95% CI: 97.0% - 100%).
The authors also reported that there was no difference in performance of HPV testing for detecting CIN 2-3 in women with and without histories of previous abnormal smears or histories of treatment for abnormal smear.

Clinical conclusions
The HPV testing resulted in referral of 31% of atypical Papanicolaou smear patients to colposcopy, 23% of whom would be CIN 2-3. 6.7% of CIN 2-3 patients would not be referred for colposcopy.

Measure of benefits used in the economic analysis
The benefit measure used in the economic analysis was the number of cases of CIN 2-3 detected with the HPV testing and this was derived from the effectiveness analysis.

Direct costs
No discounting was carried out, as the time horizon of the study was shorter than two years. The cost/resource boundary adopted was not clearly stated. Quantities of resources used were not reported and unit costs were reported for only a few items. The analysis of costs focussed on total costs of the diagnostic approach. A subgroup analysis differentiated between HPV tests performed with conventional Papanicolaou smear with a vial of specimen transport medium collected for possible HPV testing, and Papanicolaou smear using liquid-based media with HPV testing on the residual sample. Service costs included in the study were colposcopy/biopsy, incremental cost of using liquid-based media, specimen transport medium and storage, HPV test, and follow-up visits. The estimation of costs was based on actual data derived from current Health Care Finance Administration Fee Schedule and personal communications from the laboratory of the study hospital. The estimation of quantities of resources used was derived from the study and gathered from September 1997 to April 1999. The price year was 1999.

Statistical analysis of costs
No statistical analyses of costs were carried out.

Indirect Costs
Indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were not conducted.

Estimated benefits used in the economic analysis
The number of cases of CIN 2-3 detected by high-risk status HPV testing was 14. However, the result given was the total number of cases detected, which was 15. This was used to calculate cost-effectiveness.

Cost results
Total costs of the HPV approach were $73,125. The costs amounted to $67,329.93 when conventional Papanicolaou smear was performed and $60,311.32 when liquid-based media was used for Papanicolaou smear with HPV testing.

Synthesis of costs and benefits
The costs and benefits were combined by performing an average cost-effectiveness analysis. The cost per case of CIN
2-3 detected by colposcopy was $4,875 in the main analysis, $4,809.28 when conventional Papanicolaou smear was performed and $4,307.95 when liquid-based media was used for Papanicolaou smear with HPV testing.

Authors’ conclusions
The authors concluded that colposcopy should not be performed on all women with atypia on Papanicolaou smears. A diagnostic approach based on HPV testing appeared to be a reliable procedure for predicting CIN 2-3 and could reduce the number of patients referred for colposcopy. The study results also suggested that "detection of high-risk HPV infection was the only significant predictor of CIN 2-3" and no association between CIN 2-3 and several demographic and clinical characteristics was found.

CRD COMMENTARY - Selection of comparators
No explicit comparator was used in the study. However, in the effectiveness analysis, the HPV testing (both with conventional and liquid based media) was compared with the performance of colposcopy on all patients. Unfortunately, in calculating cost-effectiveness, the total number of cases detected by colposcopy was used. A proper calculation of cost-effectiveness should use the ratio of the change in number of cases detected by the change in cost of adopting colposcopy for HPV high risk only, instead of colposcopy for all. You, as a user of this database, should assess which diagnostic techniques for CIN 2-3 are currently performed in your own setting.

Validity of estimate of measure of effectiveness
The analysis of the effectiveness was conducted on the basis of a single cohort of patients, without an explicit comparison group. Blinded assessment was performed to reduce possible bias and power calculations were carried out to assess the power of the study for the detection of statistically significant differences in the study outcome. The authors noted that demographic and clinical information on patients who refused to participate in the study was not available and comparison with patients enrolled was not possible. In addition, HPV tests were conducted at colposcopy approximately 9 weeks after initial smears, therefore infection could have cleared or new infection been acquired in the interval.

Validity of estimate of measure of benefit
The benefit measure used in the economic analysis was the number of cases of CIN 2-3 detected with the HPV testing and was derived directly from the effectiveness analysis. Although this represents a widely used benefit measure in the case of diagnostic assessment of cervical cancer, the authors noted that psychological effects should also be taken into account. The authors also seemed to attribute little significance to the single case of CIN 2-3 that would be missed by stratifying by HPV risk.

Validity of estimate of costs
The perspective of the analysis was not clearly stated. Unit costs were reported for only a few items and quantities of resources used were not reported. The authors acknowledged that some costs associated with being referred to colposcopy or counselling for a cancer-positive patient were not included.

Other issues
The authors made some interesting comparisons of their findings with those from other studies. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not conducted. The authors reported some limitations of their analysis, already reported in the above fields. Results were reported fully for effectiveness, the problem with the cost-effectiveness calculation having been discussed above.

Implications of the study
The authors stated that the analysis supports the use of HPV testing for the diagnosis of CIN 2-3 and that further research should focus on the analysis of age, prior treatment, and other factors that can affect test performance. Further
analyses assessing the impact of variations in costs and levels of test performance on final cost-effectiveness analyses should be carried out. As stated in the commentary above, the authors did not perform the cost-effectiveness analysis correctly and seemed to place little significance on the loss in sensitivity by the triage method tested.

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