Human papillomavirus testing as triage for atypical squamous cells of undetermined significance and low-grade squamous intraepithelial lesions: sensitivity, specificity, and cost-effectiveness

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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
A management algorithm determining the need for colposcopy based on incorporating cytologic testing and the Food and Drug Administration (FDA)-approved human papillomavirus (HPV) Profile test (Digene Diagnostics, Silver Spring, Md, USA) in triaging patients referred with Papanicolaou smears reported as showing atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSIL). The HPV Profile is an FDA-approved HPV assay kit that measures specific binding of phosphorus 32-labelled ribonucleic acid (RNA) probes to target DNA from infected cells. The kit includes high-risk and low-risk probes.

Type of intervention
Diagnosis

Economic study type
Cost-effectiveness analysis.

Study population
Patients referred with Papanicolaou smears reported as showing ASCUS or LSIL. Women treated for cervical abnormalities within 2 years of referral were excluded from the study. Women treated for cervical intraepithelial neoplasia over 2 years before study enrolment were included.

Setting
Hospital. The economic analysis was carried out in the USA.

Dates to which data relate
Dates were not given.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.

Link between effectiveness and cost data
Costing appears to have been performed retrospectively on the same patient sample as that used in the effectiveness analysis, and was based on the number of colposcopies recommended and prevalence of grade 2 or 3 cervical intraepithelial neoplasia (CIN).

Study sample
Power calculations were not used to determine the sample size. The study sample consisted of 462 women from the study population with ASCUS or LSIL on referral Papanicolaou smears. In the study clinic, 1,128 women were evaluated with a repeat Papanicolaou smear, HPV DNA testing, and colposcopy; 1,075 underwent colposcopically directed cervical biopsies and endocervical curettage. Of these women, 462 had been referred with a Papanicolaou smear report of ASCUS or LSIL. The mean age of the women was 27.6 years (range: 14 to 75 years).

**Study design**
This was a prospective cohort study, carried out in a single centre (a colposcopy clinic serving indigent patients). The duration of the follow-up appears to have been 6 months in the cytologic testing algorithm and 6 months or 1 year, depending on the type of the results, in the HPV testing algorithm. No information appears to have been given regarding loss to follow-up. In accordance with the study protocol colposcopy, cervical biopsies, and HPV testing were performed on all women; triage for colposcopy by repeat Papanicolaou smear, or repeat Papanicolaou plus HPV screening, differed only in the criteria for colposcopy and could thus be readily compared when colposcopic examinations and high-risk HPV screening were performed on all women with ASCUS and LSIL, at the time of the repeat Papanicolaou smear taken in the Colposcopy Clinic. The physician performing colposcopy did not know the results of the HPV testing. All cytologic and biopsy specimens were reviewed by a single individual. Fifteen percent of the cytologic preparations and biopsy specimens were blindly reviewed a second time by the same individual to evaluate the consistency of interpretation of the specimens; in 90% of the cytologic specimens and 100% of the biopsy specimens the evaluations were concordant.

**Analysis of effectiveness**
The principle used in the analysis of effectiveness (intention to treat or treatment completers only) was not explicitly specified. The clinical outcomes were the percentage of patients referred for colposcopy; and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the cytology triage, high-risk HPV triage, and combined triage in detecting grade 2 or 3 CIN. Grade 2 or 3 was used as the end point for this study because most low-grade lesions will spontaneously regress even if untreated; and there is uniform agreement on the risk of invasive cancer in patients diagnosed with grade 2 or 3 CIN.

**Effectiveness results**
Colposcopy was recommended for 194 (41.9%) women on the basis of cytology triage versus 180 (38.9%) with the HPV triage and 257 (55.6%) with the combined triage.

The other outcomes were as follows:

- sensitivity was 62.7% for the cytology triage, 67.2% for the HPV triage, and 82.1% for the combined triage;
- specificity was 61.5% for the cytology triage, 65.8% for the HPV triage, and 48.9% for the combined triage;
- PPV was 21.6% for the cytology triage, 25% for the HPV triage, and 21.4% for the combined triage;
- NPV was 90.7% for the cytology triage, 92.2% for the HPV triage, and 94.1% for the combined triage.

**Clinical conclusions**
The study demonstrated that a management algorithm based on repeat Papanicolaou smear and HPV screen was nearly equivalent to the standard repeat cytologic screening triage. There was a significant improvement in sensitivity at the expense of specificity when both methods were combined.

**Measure of benefits used in the economic analysis**
The benefit measure was the number of detected cases of grade 2 or 3 CIN as identified by biopsy.
Direct costs
Costs were not discounted due to the short time frame of the cost analysis. Quantities of resource use were not reported separately from the costs, except for the number of colposcopies recommended. The cost breakdown was not reported. Cost analysis for each diagnostic procedure was based on the number of colposcopies recommended and the cost of the HPV testing. The perspective adopted in the cost analysis was not explicitly specified. The cost of colposcopy was based on Medicaid payment, while the corresponding figure for the HPV testing was based on the average cost. The price year was not reported.

Indirect Costs
Indirect costs were not considered.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analysis was carried out.

Estimated benefits used in the economic analysis
The number cases of grade 2 or 3 CIN detected by the follow-up without HPV was 42 out of 67 as identified by biopsy (62.7%).

The value for the follow-up with HPV was 45 out of 67 (67.2%) and the value for the combined triage was 55 out of 67 (82.1%).

The p-value for the comparison between the diagnostic triage with and without HPV was 0.71 (non significant).

The p-value for the comparison between the diagnostic triage without HPV and the combined triage was 0.02.

The p-value for the comparison between the diagnostic triage with HPV and the combined triage was 0.07 (non significant).

Cost results
The total cost of identifying women for colposcopy using the diagnostic procedure without HPV was $29,100. The diagnostic triage with HPV was estimated to cost $57,030. When both methods were combined, the cost amounted to $68,580.

Synthesis of costs and benefits
The cost per case identified was calculated as the cost-effectiveness ratio, resulting in $692 for the diagnostic procedure without HPV, $1,267 for the diagnostic triage with HPV, and $1,246 for the combined triage. No incremental analysis was performed.

Authors' conclusions
The Food and Drug Administration-approved HPV Profile test is not a cost-effective triage for patients referred with Papanicolaou smears reported as showing atypical squamous cells of undetermined significance or low-grade squamous lesions.

CRD COMMENTARY - Selection of comparators
A justification was given for the choice of the comparator (the routine cytology-based management); it was the standard procedure in the context in question. You, as a user of this database, should consider whether this is a widely used health technology in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness results are likely to be internally valid given the prospective nature of the study design. However, no power analysis was performed to justify the sample size. The study sample appears to have been representative of the study population (women with referral Papanicolaou smears interpreted as showing ASCUS or LSIL).

**Validity of estimate of measure of benefit**

The estimate of the health benefit measure was directly derived from the effectiveness analysis and the choice of the estimate was justified in the discussion of why low-grade lesions were not considered as the end point of the study. However, it is not entirely clear why the benefit measures, such as the number of life-years saved or quality-adjusted life-years saved (QALYs), were not adopted as the ultimate measure of benefit.

**Validity of estimate of costs**

One positive feature of the cost analysis was that some details of methods of cost estimation were given. However, the following features of the cost analysis may have adversely affected the validity of the cost results: the price year and the perspective adopted in the costs analysis were not reported; resource use data were not reported separately from the costs; statistical analysis was not performed on resource use and cost data; it is not entirely clear whether the cost data were based on true costs or on charges; the effects of the alternative diagnostic modalities on indirect costs (productivity loss) were not addressed; and the cost results may not be generalisable outside the study setting.

**Other issues**

The authors' conclusion appears to be reasonably justified given the uncertainties in the data. The issue of generalisability to other settings or countries was not addressed, although the authors did make appropriate comparisons with other studies. The issue of the degree to which the study sample was representative of the study population was explicitly addressed in the authors' comments. Incremental cost-effectiveness ratios could have been calculated, producing a more informative set of cost-effectiveness ratios. The authors noted that, at the time of the study, the Hybrid Capture technique was being used by many laboratories to screen for high-risk HPV types; the authors compared the sensitivities of the above test with the HPV Profile test in their laboratory, and the results obtained in detecting high-risk HPV types in a cross-section of women with negative biopsy results up to those showing grade 2 or 3 CIN were almost identical. The authors reported that a new Hybrid Capture Microtiter test is currently under investigation.

**Implications of the study**

The study findings suggest that, as yet, no cost-effective testing procedure of practical use, and with sufficient sensitivity, has been found for triaging patients with smears that show ASCUS or LSIL and who are most likely to have grade 2 or 3 CIN or invasive carcinoma of the cervix. It is quite possible that newer screening tests for HPV in the future will provide the degree of sensitivity necessary to be of practical value.

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**Bibliographic details**

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Other publications of related interest

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