Role of p16(INK4a) expression in identifying CIN2 or more severe lesions among HPV-positive patients referred for colposcopy after abnormal cytology


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 study examined the use of p16INK4a (p16), a cellular protein which is strongly overexpressed in dysplastic cervical cells. It may be easily revealed by immunochemistry, and thus could be considered a surrogate marker for the activated oncogene expression of high-risk human papillomavirus (HPV) in dysplastic cervical cells.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women with abnormal cytology referred to colposcopy assessment or follow-up. The analysis was restricted to patients referred to colposcopy for less severe cytology findings (LSIL or less).

Setting
The setting was secondary care. The economic study was carried out in Italy.

Dates to which data relate
The dates during which the effectiveness and resource use data were gathered were not reported. The price year was not given.

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

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were not performed. A sample of 283 women consecutively referred to the authors’ medical centre was enrolled. The women were younger than 30 years in 52 cases, aged 30 to 39 in 133 cases, 40 to 49 in 83 cases, and older than 49 in 15 cases.

Study design
This was a diagnostic study that was carried out in the Florence district in Italy. Women underwent HPV and p16 diagnostic tests prior to colposcopy assessment. No further follow-up was performed. Laboratory operators performing the testing were not aware of the outcome of the colposcopy assessment.

Analysis of effectiveness
All the patients included in the initial study sample were accounted for in the analysis of effectiveness. The primary endpoint used in the study was the accuracy of the screening strategy. The final outcome was defined according to the colposcopy-directed biopsy result (less than CIN2 or greater than CIN2) and was assumed to be negative in the presence of negative colposcopy, suggesting no biopsy. Specifically, the analysis evaluated the proportion of detected > CIN2 lesions which were HPV and p16 positive, and assessed the sensitivity, specificity, and PPV of HPV and p16 testing when used to triage to colposcopy those patients with abnormal cytology.

Effectiveness results
The distribution of patients by final outcome according to colposcopy was 174 negative, 81 CIN1/HPV, and 28 >CIN2 (CIN2 = 22; CIN3 = 6).

The PPV of different cytologic categories was 6.8% for ASCUS, 14.5% for LSIL, and 3.4% for a negative (followed up cases) report.

The HPV positivity rate was 44.2% among < CIN1 patients, 69.1% among CIN1 patients, and 89.2% among > CIN2 patients, (p<10^-6).

HPV testing had a sensitivity of 89.2% (25 of 28) for > CIN2, a specificity of 47.8% (122 of 255), and a PPV of 15.8% (25 of 158).

p16 testing was not possible in 4 cases due to inadequate material.

The p16 positivity rate was 25.3% among < CIN1 patients, 57.4% among CIN1 patients, and 88.0% among > CIN2 patients, (p<10^-6).

All CIN3 cases were positive at p16 testing.

The sensitivity for > CIN2 was 88.0% (22 of 25), the specificity was 61.2% (79 of 129), and the PPV was 30.5% (22 of 72).

Clinical conclusions
The effectiveness analysis showed that p16 testing of HPV-positive cases showed a relatively good sensitivity and a double PPV compared with HPV testing, but the detection rate for > CIN2 was reduced by 21.5%.

Measure of benefits used in the economic analysis
The summary benefit measure was the number of cases of CIN 2 or 3 detected. This was derived directly from the effectiveness analysis.

Direct costs
The perspective of the analysis was not explicitly stated, but it might have been that of the third-party payer. The analysis included the costs associated with colposcopy, punch biopsy plus histology, HPV testing and the p16 test. The unit costs and the quantities of resources used were presented separately. The costs were derived from Italian National Health Service current tariffs. Resource use was based on the number of patients included in the effectiveness study. Discounting was not relevant as the costs were incurred during a short time. The price year was not reported.
Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered.

Currency
Euros (EUR).

Sensitivity analysis
Sensitivity analyses were not performed.

Estimated benefits used in the economic analysis
The number of cases of CIN 2 or 3 detected was 28 when using ASCUS/LSIL criteria to prompt colposcopy, 25 with HPV testing, and 22 with HPV/p16 testing.

Cost results
The total costs were EUR 11,700 with ASCUS/LSIL, EUR 15,330 with HPV testing, and EUR 15,490 with HPV/p16 testing.

The cost per assessed woman was EUR 41.34 with ASCUS/LSIL, EUR 54.16 with HPV testing, and EUR 54.73 with HPV/p16 testing.

Synthesis of costs and benefits
Average cost-effectiveness ratios were calculated in order to combine the costs and benefits of the alternative strategies.

The average cost per >CIN2 detected was EUR 417.85 with ASCUS/LSIL, EUR 613.20 with HPV testing, and EUR 704.09 with HPV/p16 testing.

An incremental analysis was not carried out. However, the conventional strategy was dominant since it was both more effective and less expensive than the alternative strategies.

Authors' conclusions
Triage by human papillomavirus (HPV) and p16INK4a (p16) improved the accuracy of diagnostic assessment in women with abnormal cytology, but decreased the detection rate for cervical intraepithelial neoplasia (CIN >2). It was associated with substantially higher costs than the conventional screening strategy in Italy.

CRD COMMENTARY - Selection of comparators
The reason for the selection of the comparators was clear in that the conventional screening programme was compared with two alternative strategies. The two alternatives were accurately described. Colposcopy was considered the ‘gold’ standard, although the authors noted some limitations of this diagnostic approach. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were derived from a diagnostic study. Thus, a single group of patients was enrolled and underwent all screening strategies. Such a design has the advantage of applying both the comparator and the new
interventions to the same sample of patients. Since a control group was not required, this reduces the potential impact of selection bias and confounding factors. The selection of patients was not randomised but consecutive cases were enrolled, which represents a strength of the analysis. Investigators blinded to the final outcome performed the tests independently, thereby limiting the effect of assessment bias. No justification for the size of the sample was provided and it was unclear whether the sample was representative of the population of women with abnormal cytologic results. These issues should be considered when assessing the validity of the effectiveness analysis.

**Validity of estimate of measure of benefit**
The summary benefit measure was specific to the disease considered in the study. It is not comparable with the benefits of other care interventions. However, the number of cases detected represents a widely used measure for screening programmes.

**Validity of estimate of costs**
The analysis of the costs appears to have been performed from the perspective of the third-party payer, although this was not explicitly stated. The costs were derived from national tariffs. Details of the unit costs and resource quantities were presented, which enhances the possibility of replicating the analysis in other settings. Statistical analyses of the costs were not carried out and the use of alternative cost estimates was not investigated. The price year was not reported, which will make reflation exercises in other time periods difficult.

**Other issues**
The authors stated that their findings, especially those related to the clinical analysis, were comparable with those from other studies. In terms of generalisability of the study results to other settings, the authors stated that the cost analysis reflected the Italian context, in which the cost of colposcopy is quite low relative to the other diagnostic procedure. However, the results may not be valid for other health systems. The study referred to women with abnormal cytologic results and this was reflected in the authors’ conclusions.

**Implications of the study**
The study results do not support the use of p16 testing as a primary screening tool in women with abnormal cytologic results. The authors noted that reductions in the cost of molecular testing could make p16 a more cost-effective strategy.

**Source of funding**
None stated.

**Bibliographic details**

**PubMedID**
16411180

**DOI**
10.1002/cncr.21713

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**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Cervical Intraepithelial Neoplasia /chemistry /diagnosis /pathology /virology; Cervix Uteri /chemistry /pathology /virology; Colposcopy /economics; Cyclin-Dependent Kinase Inhibitor p16 /analysis /genetics; DNA, Viral /analysis /genetics; Female; Humans; Immunohistochemistry; Middle Aged; Papillomaviridae /genetics /isolation & purification; Papillomavirus Infections /diagnosis /genetics /pathology; Polymerase Chain Reaction; Predictive Value of Tests; Sensitivity and Specificity; Uterine Cervical Neoplasms /chemistry /diagnosis /pathology /virology

**AccessionNumber**
22006006367

**Date bibliographic record published**
30/04/2007

**Date abstract record published**
30/04/2007