*Health Technology Assessment* 1999; Vol. 3: No. 14 (Executive summary)

**Review**

## *Executive summary*

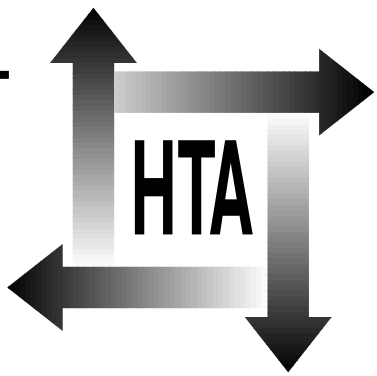
# A systematic review of the role of human papillomavirus testing within a cervical screening programme

J Cuzick[1*]
P Sasieni[1]
P Davies[2]
J Adams[1]
C Normand[3]
A Frater[3]
M van Ballegooijen[4]
E van den Akker[4]

[1] Department of Mathematics, Statistics and Epidemiology, Imperial Cancer Research Fund, London, UK
[2] Molecular Diagnostics Ltd, London, UK
[3] Department of Public Health and Policy, Health Services Research Unit, London School of Hygiene and Tropical Medicine, UK
[4] Faculty of Medicine and Health Sciences, Erasmus Universiteit, Rotterdam, The Netherlands

[*] Corresponding author

**Health Technology Assessment**
**NHS R&D HTA Programme**



# Executive summary

## Background

It is timely to consider the role of human papillomavirus (HPV) testing within the cervical screening programme. A plateau of what can be achieved by conventional cytology is now being reached, and the fundamental importance of HPV in the aetiology of cervical cancer has been clearly demonstrated. There is much interest in the use of HPV testing to improve both the effectiveness and cost-effectiveness of cervical screening. It is thus opportune to review research into its potential implementation. Since the field is currently very active there is considerable flux in the state of knowledge, so that the current literature will quickly become obsolete.

## Objectives

(1) To evaluate the available data concerning the role of HPV testing:
   (a) in primary screening, either alone or as an adjunct to cytology
   (b) to improve the management of women with low-grade cytological abnormalities
   (c) to improve the accuracy of follow-up after treatment of preinvasive or early invasive lesions.

(2) To review the methods available for HPV testing and determine their appropriateness for widespread implementation.

(3) To determine what future research is required to obtain more reliable answers about its use in screening.

## Methods

Eight databases were searched, producing a total of about 2100 papers. Additional references were sought by scanning the citations of review articles and books devoted to HPV. Ongoing and unpublished studies were included.

Papers were divided into broad categories and initially screened by title and abstract using predefined criteria. Complete copies of papers not rejected were obtained, and data were abstracted. Abstractions were done by one author and checked by another. Tabular, graphical and textual material was used to synthesise the data.

## Results

### Testing methodology

A range of approaches have been used to detect HPV in smear material with widely differing results. The most thoroughly studied methods are now being superseded by newer methods which offer better sensitivity, specificity and reproducibility and are easier to perform. However, many of the most relevant studies are just beginning to reach the literature, and most of the large studies related to screening are still ongoing with at most only preliminary reports available. Currently, two consensus primer systems – the MY09/11 and the GP5+/6+ pairs – and the second-generation hybrid capture system (HC-II) would seem to be the methods of choice. These three methods all have high absolute sensitivity for detecting oncogenic viruses and have the potential for automation. Developments in the form of second-stage assays, may help improve specificity without substantially reducing sensitivity.

### Natural history

HPV is a sexually transmitted disease with peak incidence in the age band 20–24 years which gradually declines up to about the age of 40–45 years, but then may begin to increase slowly again. Most infections are transient, with a median duration of at most 12 months, and pose no risk of cervical neoplasia: only the 10–20% that remain persistent are of concern. Evidence of infection, either by serology in stored blood samples or in fixed archival tissues, is found many years before serious disease is present, and indicates that infection precedes disease. Detection of HPV DNA in the absence of cytological abnormalities can also indicate presence of high-grade cervical intraepithelial neoplasia (CIN) which was missed by cytology. Women with minor cytological abnormalities who test negative for oncogenic HPV have a low risk of developing high-grade CIN within 3 years.

### Prevalence

With modern tests, over 95% of all cervical cancers are HPV-positive, and 75–95% of high-grade CIN lesions are associated with a positive HPV test on exfoliated cells. In comparative studies, HPV testing has a greater sensitivity for CIN II/III than cytology. Greater variability in the HPV positivity rate of 'normal' populations is seen, ranging from 3 to 20%, or more in some studies, leading to concern about specificity. This variability reflects a number of factors, including age, extent of sexual exposure, previous disease, and type of assay used.

### Potential roles in screening

The most appropriate group in which to initially consider the role of HPV testing as part of primary screening is in women aged 35 years or more, for whom false-positive rates are lowest. HPV testing may also have other roles within the screening programme. The most obvious is in improving the management of women with low-grade or borderline smears. In this context, HPV testing can help identify which women are in need of immediate referral for colposcopy. However, there is still uncertainty about the negative predictive value, and the safety associated with reduced surveillance in HPV-negative women. HPV testing has also been proposed for post-treatment surveillance of CIN, and early cancer, to monitor for complete excision. Early results look very promising, but more, better designed studies are needed here.

### Modelling

A number of possibilities exist for introducing HPV testing at different ages and at different screening intervals. It could be used as the sole primary screening modality, as an adjunct to cytology, or in the triage of borderline and mild dyskaryosis. Published modelling studies are limited by the estimates of effectiveness, which are only now becoming available, and the cost of the test, which is still not known for high-volume applications. New modelling studies are presented based on the MISCAN micro-simulation programme, using costs based on the British programme, and disease models based on the natural history of HPV related cervical cancer. In the time available, only baseline calculations could be performed. These were sufficient to show that current knowledge is inadequate for assessing cost-effectiveness. The results of the modelling work show that for plausible values of prevalence, screening sensitivities and progression, HPV testing may be effective and cost-effective. For plausible assumptions about the model parameters, there are uses of HPV testing that would provide benefits at a lower cost than many existing healthcare programmes. However, the wide range of results that come from using high and low estimates for these parameters show that more data are needed to refine modelling using more accurate estimates of key parameters.

### Economic issues

A range of economic issues related to introducing HPV screening were surveyed as well as the very sparse literature on psychosocial aspects. In neither case is the database adequate to draw firm conclusions.

## Conclusions and recommendations

HPV testing is more sensitive than cytology for high-grade CIN, but has lower specificity, especially in young women. HPV testing cannot currently be recommended for widespread implementation. The evidence suggests it may be appropriate in certain limited situations such as the management of borderline smears or in older women when regular screening is problematic, so that high sensitivity is needed.

Full evaluation of HPV testing should provide information on the length of protection after a negative result, and consideration should be given to a very large trial with a reduction in cancer incidence as the end-point. Further studies and modelling simulations are needed to evaluate the range of potential roles and most cost-effective use of HPV testing, and how it should be implemented and integrated with other testing methodologies.

## Publication

Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al.* A systematic review of the role of human papillomavirus testing within a cervical screening programme. *Health Technol Assess* 1999;**3**(14).

# NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Population Screening Panel and funded as project number 98/04/01.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

Series Editors: Andrew Stevens, Ruairidh Milne and Ken Stein
Editorial Assistant: Melanie Corris

The editors have tried to ensure the accuracy of this report but cannot accept responsibility for any errors or omissions. They would like to thank the referees for their constructive comments on the draft document.

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 1703 595 639 Email: hta@soton.ac.uk
http://www.hta.nhsweb.nhs.uk ISSN 1366-5278