

EVALUATION OF SENTINEL SITES
FOR HPV TRIAGE AND TEST OF CURE

Report to the NHS Cancer Screening Programmes

September 2011

Authorship

Epidemiology – Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Dr Sue Moss
Rachel Kelly

Health Economics - London School of Hygiene and Tropical Medicine

Dr Rosa Legood
Dr Zia Sadique

Modelling HPV test of cure – Cancer Council New South Wales, Australia.

Dr Karen Canfell,
Jie Bin Lew,
Megan Smith,
Robert Walker.

Acknowledgements

This evaluation was funded by NHS Cancer Screening Programmes, and conducted on behalf of the HPV Special Interest Group*

* List of group members.

Patnick J¹, Kitchener H², Albrow R², Bailey A³, Cubie H⁴, Denton K⁵, Desai M⁶, Ellis K⁷, Evans C⁸, Ferry M⁹, Fisher A¹⁰, Frew V¹¹, Giles T⁸, Howell-Jones R¹², Hunt K⁵, Levine T¹³, Lonsdale R¹⁰, Marshall J⁶, Medlock J¹⁴, Moore C⁴, Muir P¹⁵, Rimmer J¹, Sargent A³, Smith JHF⁷, Soldan K¹², Tidy J⁷, Turnbull L⁸, Turner A¹⁶, Walker P¹⁷, Winder R¹, Young M¹⁷

1. NHS Cancer Screening Programmes, Sheffield
2. School of Cancer Studies and Enabling Sciences, University of Manchester, Manchester Academic Health Science Centre
3. HPA Manchester
4. Scottish HPV Reference Laboratory, Edinburgh
5. Southmead Hospital, Bristol
6. Central Manchester University Hospitals NHS Foundation Trust
7. Sheffield Teaching Hospitals NHS Foundation Trust
8. Royal Liverpool University Hospital
9. North West London Hospitals NHS Trust
10. Queen Elizabeth Hospital, Gateshead
11. Norfolk & Norwich University Hospital
12. Health Protection Agency
13. North West London Hospitals NHS Trust
14. University Hospital Aintree
15. HPA South West Regional Laboratory, Bristol
16. Manchester Royal Infirmary
17. Royal Free Hospital

We are grateful to Professor Alastair Gray for his comments on this report.

EXECUTIVE SUMMARY

Epidemiology Results

- The evaluation of the HPV/LBC Cervical Screening Pilot studies conducted in 2001 showed that introducing HPV triage into the NHS Cervical Screening Programme was feasible, acceptable and cost effective in terms of quality and of life years saved. The present study considers the wider roll out of HPV triage at six ‘Sentinel’ sites throughout England.
- All women aged 25-64 with routine cytology reported as borderline or mild dyskaryosis were eligible for inclusion. Women who tested negative for HPV were returned to routine recall; those who tested positive were referred for colposcopy.
- Women treated for CIN had a ‘test of cure’ cytology at six months, if this was negative then women were tested for HPV to determine management.
- Test of cure was also evaluated in non-triaged women treated for CIN following high grade or persistent low grade cytology; a cytology test was performed six months after treatment, if borderline changes or worse were found the woman was referred to colposcopy. If the cytology was a negative an HPV test was performed; if this was positive the woman was referred to colposcopy, if negative the woman was returned to routine recall.
- Two sites used BD SurePath™ LBC, three used ThinPrep® LBC, and one site used both; HPV testing was carried out at two laboratories.

HPV as a triage for women with borderline or mild dyskaryosis

- 10051 women were eligible for inclusion into the study; 6507 with borderline cytology and 3544 with mild dyskaryosis.
- HPV positive rates were higher than those observed in the earlier HPV/LBC Pilot studies; 53.7% in women with borderline cytology and 83.9% for women with mild dyskaryosis were HPV positive compared to 45.6% and 82.6% respectively in the earlier studies. This may reflect differences between the sites taking part in the two studies.
- HPV positive rates were higher in the sites using ThinPrep® LBC than in those using BD SurePath™ LBC: however this may reflect differences between the sites rather than the technology used. In sites using both technologies no difference was observed between the two.
- HPV positive rates decreased with increasing age; consequently women attending for a first routine test had higher HPV positive rates than those returning for a routine recall test.
- The mean and median RLU values decreased with decreasing age, and were higher in women with mild dyskaryosis than in women with borderline dyskaryosis in every age group.
- The overall rate of referral to colposcopy was higher in the current study than for either the initial or revised protocol of the earlier HPV/LBC Pilot sites. In women with borderline cytology the rate of referral was significantly higher in the current Sentinel sites study due to the higher HPV positive rate. In women with mild dyskaryosis the rate of referral was higher

in the Sentinel sites study than for the earlier HPV/LBC Pilot studies under the revised protocol, in which HPV positive women aged 20-34 were retested at 6 months.

- Ninety percent (5838/6470) of HPV positive women attended colposcopy; of these 96.5% had a known satisfactory colposcopy outcome.
- Of those HPV positive women who attended colposcopy 54.6% were negative, 16.3% had CIN2 or worse and 6.1% had CIN3 or worse. There were 3 cases of cervical cancer, all in women aged 25-34.
- 62% of HPV positive women who attended colposcopy underwent a punch biopsy; 49.0% of these had a negative histology. A further 3.4% of HPV positive women who attended colposcopy had an excision biopsy, of which 28.6% did not show any CIN.
- There were 1329 cases of CIN1; 32.9% were not treated but had a repeat test at 12 months, and 2.7% (n=36) were treated and then underwent a test of cure cytology at six months and if negative an HPV test. However in women with at least 12 months follow up, 64.4% had repeat cytology at 12 months, 4.0% were treated and underwent test of cure at 6 months, and 30.8% had no known management. Among those who attended for cytology at twelve months the rate of moderate or worse dyskaryosis was 3.4%.
- The results suggest that the HPV positive rate was higher in women with borderline cytology who had the presence of koilocytes recorded than all women with borderline changes, however the numbers were too small to draw definitive conclusions. Similarly the numbers of women with borderline abnormalities in glandular cells were too small to use.

HPV as a ‘test of cure’

- In addition to the 36 women with CIN1 a further 222 women with CIN2 and 158 women with CIN3 or worse were treated and then attended a 6 month test of cure. Of these, 25.7% (107/416) ‘failed’ test of cure; 15.6% due to an abnormal cytology and 10.1% due to a positive HPV test. The rate of failure decreased with increasing severity of CIN grade treated.
- Of the 107 women who failed test of cure, 41 attended a subsequent colposcopy; 65.9% of women were negative for CIN, however 12.2% tested positive for CIN2 or worse.
- The non-triage test of cure arm contained 3203 women who had previously been treated for CIN due to a history of high grade cytology or persistent low grade cytology; 60.5% of women had been treated for CIN3.
- 18.3% of women failed test of cure; 6.2% failed due to an abnormal cytology and 12.2% failed due to a negative cytology but a positive HPV test. The failure rate was highest in women treated for CIN1.
- Of the women who failed test of cure 74.7% attended subsequent colposcopy. At colposcopy 6.9% of women had CIN2 or worse detected, however the majority of these cases of high grade CIN were in women who had failed due to an abnormal cytology, as opposed to a positive HPV test.
- Overall the positive predictive value of HPV infection in cytologically negative women for detecting residual CIN3 or worse is 0.4%, for detection of CIN2 or worse it is 2.9%.

Results of the Economic Analysis

An economic analysis was undertaken to evaluate the costs and outcomes associated with using HPV as a triage for women with borderline or mild dyskaryosis, and using HPV as a test of cure. The following costs were included in the analysis: training and implementation; administration, identifying samples/specimen reception and transport; as well as the cost of HPV testing. The literature was reviewed to identify studies evaluating patient preferences and utilities. Modelling work was undertaken on the cost-effectiveness and workload implications of HPV testing, focusing particularly on HPV as a test of cure. Outcomes in the economic evaluation were defined mainly in terms of cases of CIN3+ detected, and hence incremental cost-effectiveness was defined as the cost per CIN3+ case detected.

- As part of the implementation project, training was provided in primary care, and for HPV testing staff and cytology laboratory staff responsible for identifying samples requiring tests. The majority of this training was undertaken in-house; it is anticipated that the costs of primary care training could be incorporated within routine training updates. The main implementation component for the cytology laboratories was making changes to the Information Technology system.
- A 'hub and spoke' delivery model was used at most of the sites within the Sentinel sites study with two HPV processing centres providing HPV testing across six sites. The average transport costs per sample across the sites located approximately 50KM away was £0.44 (range £0.38 to £0.50). For those sites located further from the HPV processing laboratory (150-300KM), average transport costs per sample were higher at £2.76 (range £2.20-£3.33).
- One of the HPV processing centres was set-up within an existing cytology laboratory, in an 'integrated cytology/HPV laboratory'. The costs of administration, identifying samples/specimen reception and transport with the 'integrated laboratory' were compared with a 'hub and spoke' approach where cytology laboratories sent samples for processing elsewhere. We found that the 'integrated laboratory' was cheaper than the 'hub and spoke model'. The additional cost per HPV sample of administration, staff time and transport where HPV tests were sent off for processing, compared to an integrated model, ranged from £2.54 to £4.86 depending on the transport distance.
- The cost of HPV testing includes the cost of equipment, consumables, maintenance, and staff time. These costs all increase when running smaller batches. These costs varied depending on the batch size from £12.83 (88 samples per run) to £20.97 (22 samples per run). However, the increase in average cost for running 66 samples at a time compared to 88 was only an additional £1.20 per sample.
- To meet government targets, it is essential that HPV testing can be integrated within the overall two week turn-around times from a cytology sample being taken to a woman receiving the result. This was achieved at some sites within the Sentinel Sites study with a twice weekly HPV testing schedule where overall initiatives had been put in place to increase turn-around times - for even faster turn-around times a further option would be to run tests daily.
- Running daily HPV testing with full batches is only possible with an HPV processing centre that serves a group of cytology laboratories reading over 300,000 slides per year. An alternative would be to have one National laboratory. However, the results of this project suggest that transport costs are significantly higher over longer distances. Nevertheless, a

further potential advantage of processing HPV tests at higher volumes is the potential to generate savings from economies of scale. For example, further HPV equipment could be used that increases the automation of the HPV testing process.

- Based on running HPV tests twice a week, it is possible to run full HPV testing batches with two testing centres per SHA. This may be a cost-effective option if transport costs are reduced, especially where the SHA covers a large geographic area.
- The published literature was reviewed to identify women's preferences for HPV testing. The majority of the studies indicate that women prefer HPV testing to repeat smear tests. The studies indicate that although there may be a negative emotional effect associated with receiving a positive HPV test result, this is essentially short-term and is not apparent beyond six months. No statistically significant differences in utility scores were identified between alternative management strategies.
- Given the loss to follow-up with repeat cytology, risk of progression with delayed follow-up and women's preferences, HPV triage is likely to be a highly cost-effective option compared to repeat cytology.
- Modelling work within the HPV implementation project has mainly focussed on using HPV testing as a 'test of cure', as there has been limited evaluation of this topic to date. The results suggest that using HPV testing to manage women treated for CIN was cost saving compared to current management based on surveillance with cytology and colposcopy. The modelling also indicated that over a 10 year time horizon more cases of CIN3+ are averted utilising strategies using HPV test of cure compared with current practice suggesting that HPV test of cure is a highly cost-effective option.
- A limitation of the 'HPV test of cure' modelling work is that predictions for detected CIN2/3+ recurrence over the first 10 years post-treatment are extrapolations based on data from studies with shorter follow-up periods, and are therefore not guarantees of safety. As cancer is a rarer outcome compared to CIN3, a reduction in CIN3+ does not necessarily imply a reduction in cancer cases.

Conclusions

Rates of referral to colposcopy increase with the introduction of HPV triage but the rates vary between sites, probably due to differences in classification of cytology. Triage would allow approximately a third of all borderline and mildly dyskaryotic women to be returned immediately to routine recall, thus reducing the burden on cytology services. The positive predictive value of a positive HPV test in those women for CIN2 or worse observed in this study was 16%, but again there will be variation between sites., resulting in variation in colposcopy workload.

HPV testing on women with negative cytology as a test of cure had a low PPV for high grade CIN. However it allows the majority of women who are negative for HPV to be returned directly to routine recall, by passing the long management process normally associated with follow up after treatment.

To be cost-efficient, and to meet turn-around times, HPV testing needs to be conducted at HPV testing centres with sufficient throughput to run full batches of HPV tests. Running daily batches, this would only be possible with an HPV testing centre serving a group of cytology laboratories reading over 300,000 slides annually.. As savings can be generated by implementing HPV testing within a cytology laboratory compared with a 'hub and spoke' delivery model consideration should be given to this implementation option.

Taking into consideration the loss to follow-up with repeat cytology, risk of progression with delayed follow-up and women's preferences, HPV triage is likely to be a highly cost-effective option compared to repeat cytology.

Modelling of HPV test of cure would generate cost saving compared with current colposcopy management due to a reduction in colposcopy workload and is also slightly more effective at averting cases of CIN3+. Therefore, this is a highly cost-effective policy option.

1. INTRODUCTION

1.1 Cervical Cancer

Cervical cancer is the second most common cancer among women; worldwide it affects around 500,000 women annually. The majority of these cases occur in the developing world, however there is still a threat from cervical cancer in the UK; 2321 new cases were diagnosed in England in 2006¹.

The introduction of an organised screening programme in the UK in 1988 has led directly to the fall in the number of new cases annually. The cervical screening programme has been estimated to prevent up to 3,900 cases of cervical cancer^{1,2} and save approximately 4,500 lives per year³. Despite these successes there is a constant drive to improve the cervical screening programme in part through advances in technology and science.

Infection with high risk Human Papillomavirus (HPV) is now known to be a necessary aetiological factor in the development of cervical cancer⁴.

Those strains of HPV, associated with genital tract infection are subdivided into high and low risk types, and of the former HPV 16 and 18 are estimated to be responsible for about 70% of all cases of cervical cancer⁵.

HPV infection with high risk types can be detected using DNA amplification methods. One such test is The Hybrid Capture 2 assay (HC 2) (Digene Corporation, Gaithersburg, Md.) which detects 13 cancer-associated HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68⁶.

1.2 HPV triage

Infection with at least one strain of HPV is very common; however testing for a high risk HPV DNA strain using HC2 can help distinguish women who are at a high risk of disease from those at a very low risk amongst women with equivocal findings at cytology. A meta-analysis has found that the use of HPV testing for triage in this way improved the accuracy for ASCUS samples for an outcome of CIN2 or worse compared with repeat cytology⁷.

1.3 The HPV/LBC Pilot studies

In 2001, HPV/LBC pilot studies of the feasibility of introducing HPV triage in the English screening programme were started. Three sites in England converted to using liquid based cytology (LBC) and HPV triage for women with borderline or mild dyskaryosis. Under the original protocol all women who tested positive for HPV were referred for colposcopic examination. Women who tested negative were retested at six months, and referred to colposcopy if HPV positive or cytologically abnormal. However this was altered mid-way through the pilot period in two of the sites, when it became clear that the rate of HPV positivity among younger women was causing an unacceptable workload of colposcopy referrals. Subsequently HPV positive women aged 20-34 were managed by repeat cytology and HPV testing at 6 months, and referred for colposcopy only if HPV infection and/or cytological abnormality persisted.

The results of this study suggested that while introducing HPV triage decreased the number of repeat cytology tests and reduced the time taken to return women to routine recall, it also resulted in a large increase in referrals to colposcopy. It was concluded that adding HPV triage to LBC screening was feasible, acceptable to women and cost effective both in terms of quality and of life years saved^{8,9}. However concern remained about the substantial increase in colposcopy referrals with HPV triage. An analysis including a further three years of additional data carried out in 2008 confirmed findings of the original report.

1.4 HPV testing as a ‘Test of Cure’

Recent evidence has shown that it is also possible for HPV testing to play a role in the follow up period after treatment for CIN. Testing for HPV can be used to determine if women who have been treated for high grade CIN harbour residual disease, as the likelihood of developing CIN2 or worse in the absence of HPV DNA is low¹⁰. The sensitivity of HPV testing for detecting treatment failures is estimated to be high, similar to the sensitivity of HPV testing in primary diagnosis; some studies have found a sensitivity of up to 100%¹¹.

Predicting treatment failure would be beneficial both to the screening programme and to women, as current post-treatment regimes in the UK require monitoring every six months for two years and annual testing for 10 years after treatment. HPV test of cure at six months could return treated HPV negative women immediately back to routine 3 year recall.

1.5 The Sentinel sites study

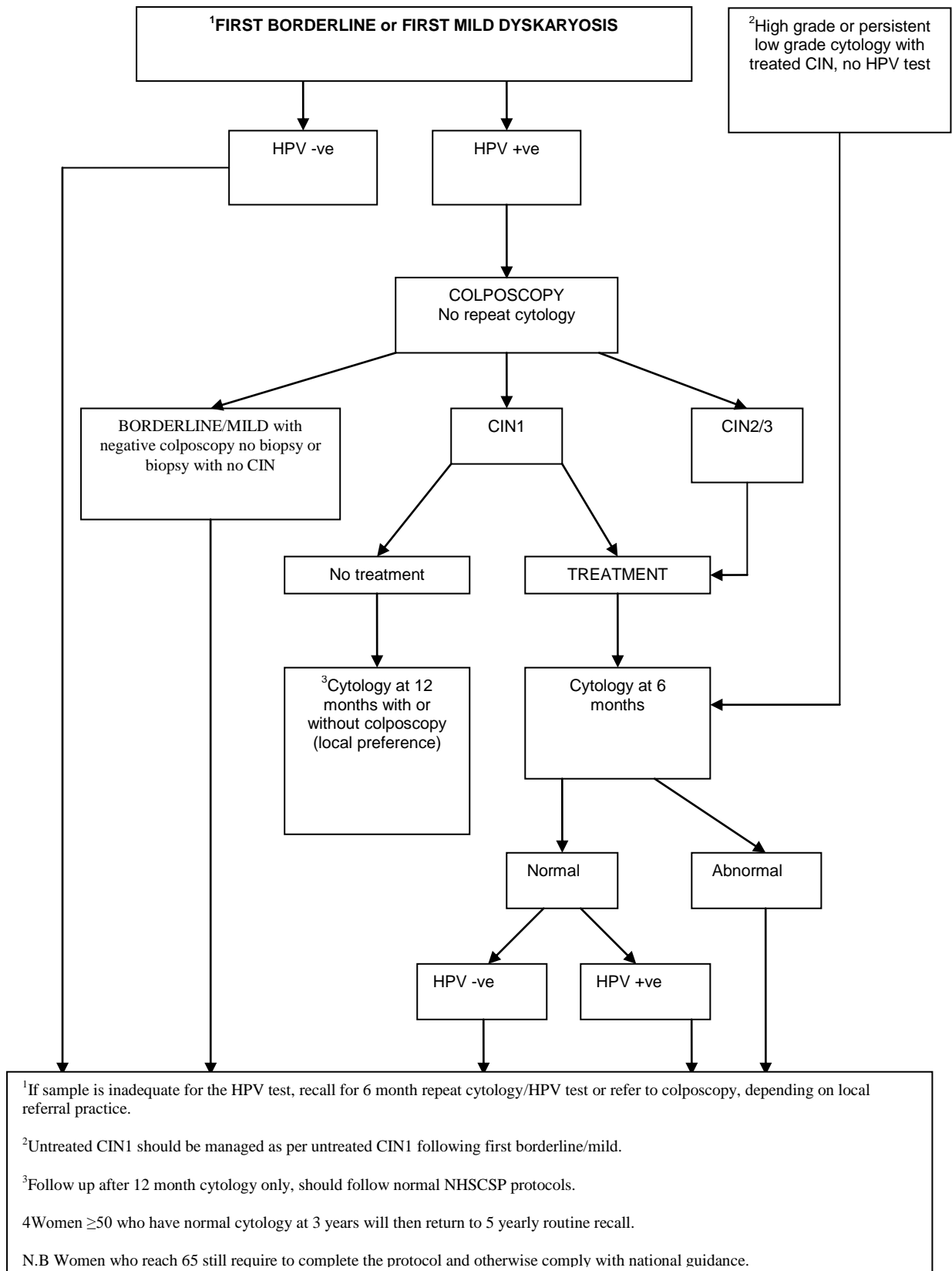
Following the evaluation of the earlier HPV/LBC Pilot studies, six ‘Sentinel sites’ were established to follow an agreed protocol for the use of HPV triage for women with borderline or mild dyskaryosis, and HPV testing as a test of cure for women with treated CIN. The sites included two of the original pilot sites, Bristol and Norwich, together with four additional sites; Liverpool, Manchester, Northwick Park and Sheffield. Together these six sites represent approximately 10% of the English cervical screening programme. All women aged 25-64 with routine cytology reported as borderline or mild dyskaryosis were eligible for inclusion in the study. Women who tested negative for HPV were returned to routine recall at three or five years depending on their age, and no further information was collected; women who tested positive were referred for a colposcopic examination.

Cytology was liquid based, and once a borderline or mild result had been identified the cytology sample was sent to one of two HPV testing laboratories. The six sites used two different technologies for liquid based cytology (LBC); Bristol, Northwick Park and Norwich used ThinPrep[®] LBC HPV testing for all three sites was performed in Bristol. Liverpool and Sheffield used BD SurePath[™] LBC and Manchester used both technologies; HPV testing for these three sites was performed in Manchester. A cut off of 2RLU/Co using the Qiagen Hybrid capture 2 assay was used to determine positivity.

The ‘test of cure’ investigation comprised of two parts; the triage arm and the non-triage arm. The triage arm included women who tested positive for HPV and were diagnosed with CIN at colposcopy. These women were treated and then underwent ‘test of cure’. The test of cure non-triage arm included women who had not come through the triage route, who had been treated for CIN following high grade or persistent low grade cytology, who then underwent ‘test of cure’. Six months after treatment women returned for cytology; if this showed borderline or worse dyskaryosis they were immediately referred to colposcopy. If the cytology was normal the women were tested for HPV, and if positive referred to colposcopy. Women who were negative at cytology and HPV testing were returned to routine recall.

This study aimed to confirm and expand the findings of the HPV/LBC Pilot studies and provide a new cost-effectiveness analysis. The study protocol is shown in figure 1.

Figure 1 Study protocol



The epidemiological evaluation was carried out by the Cancer Screening Evaluation Unit (CSEU), and the economic evaluation by researchers at the London School of Hygiene and Tropical Medicine (LSHTM).

The main aims of the epidemiological evaluation were:

- to study outcomes from the Sentinel sites study in order to estimate the likely impact of wider roll out of HPV triage, in particular
 - HPV positivity rates
 - rates of referral to colposcopy
 - attendance rates at colposcopy
 - outcome of colposcopy in HPV positive women
 - outcome in women with CIN1 at colposcopy who were not treated
- to estimate the positive predictive value of HPV triage
- to consider the use of HPV testing as a test of cure after treatment of CIN, in particular
 - the rate of treatment failure
 - outcome in women with abnormal cytology at test of cure
 - outcome in women with normal cytology who are HPV positive at test of cure

Subsidiary aims include:

- to examine compare HPV positive rates associated with different liquid based cytology technologies
- to examine the colposcopy procedures being used in the Sentinel sites
- to consider the effect of classifying samples which contain koilocytes (currently reported as borderline changes) as mild dyskaryosis

1.6 Outline of the report

In section 2 the methods of data collection are described. Section 3 presents the results of the epidemiological evaluation of HPV triage, and section 4 the evaluation of the use of HPV testing as a 'test of cure'. Section 5 reports the available data on the presence of koilocytes in cytological samples. Section 5 describes the methods used for the economic evaluation and the results of this are presented in section 6, section 7 contains an overall discussion of the evaluation results.

2. DATA COLLECTION

2.1 Individual data

Women were identified using a unique identifier generated by the sites and by dates of birth; no NHS numbers or names were used. The Sentinel sites were asked to identify eligible women and to record their management and outcomes in a spreadsheet constructed by the CSEU.

The spreadsheet was used to collect data on relevant cytology results, HPV test results, RLU values, biopsy, treatment and histology and the corresponding dates at each of six distinct steps. Information on management and reasons for non-attendance was also requested.

The data collected included:

Step 1; Initial borderline or mildly dyskaryotic cytology

Initial cytology result, HPV test result and RLU value.

Step 2; Colposcopy

Colposcopy results for women who were positive for HPV at step 1, and the type of biopsy performed.

Step 3a; Repeat cytology results

Repeat cytology results for those women who had CIN1 detected at step 2 colposcopy and were not treated, but have a repeat cytology at twelve months.

Step 3b; Repeat cytology results after treatment

Test of cure triage arm; the treatment histology and test of cure results for women who have CIN 1, 2 or 3 at colposcopy and are treated.

Step 4; Repeat colposcopy results

Colposcopy results for women with an abnormal cytology or positive HPV test at step 3b test of cure.

Test of cure non triage arm

Women in the test of cure non-triage arm undergo a test of cure cytology six months after treatment. If this is abnormal, or normal but HPV+, they will also be referred to colposcopy at step 4.

Sites were requested to return completed databases at six month intervals. These were entered into a master database for analysis purposes.

Data collection period

Entry into step 1 ran from 01/01/2008 until 01/04/2009. However some sites did not begin the protocol until March 2008; the last site to begin the protocol was Liverpool, where the study commenced in June 2008. Follow up data for all steps were collected until September 2009. Requests for individual data were then made for women who would have been expected to have had further management by this point.

3. EPIDEMIOLOGICAL EVALUATION OF HPV AS A TRIAGE FOR BORDERLINE AND MILD DYSKARYOSIS

This section presents the results of the first three steps of the protocol; initial cytology and HPV results, subsequent colposcopy results in those who were HPV positive and 12 month cytology results in women with untreated CIN1 at colposcopy.

Women who were under 25 years or over 64 years at the time of cytology were excluded from analysis. According to the protocol all women with a first test reported as borderline or mild dyskaryosis were eligible. Analysis was not restricted by reason for cytology because this was coded as previous abnormal, previous treatment etc. if a woman has had an abnormal test result or treatment anywhere in her screening history. The sites only provided data on women they knew to be eligible. Therefore 3022 women for whom reason for cytology was not coded as routine call or recall were included.

In total 10051 eligible women entered the study; 6507 (64.7%) had an initial borderline test and 3544 (35.3%) had initial mild dyskaryosis.

Results are presented for all 6 sites combined unless specified.

3.1 HPV positive rates

Table 3.1.1 gives the proportion of women who were positive for HPV, based on an RLU value of 2RLU/Co, by age group and initial cytology result. The overall positive rate was 53.7% in women with a borderline test and 83.9% in women with mild dyskaryosis. There was a highly significant decreasing trend in HPV positive rate with increasing age ($p < 0.0001$) which was observed both in women with borderline cytology and those with mild dyskaryosis.

Despite the lower age limit for the NHSCSP being increased from 20 to 25 years in 2003, the rates observed were greater than those in the earlier pilot project, which were 45.6% and 82.6% for women with borderline cytology and mild dyskaryosis respectively.

The rates of HPV positivity varied between sites, ranging from 34.8% to 73.3% for women with borderline cytology, and from 73.4% to 91.6% for women with mild dyskaryosis. These differences remained after the rates were standardised for age (Table 3.1.2).

A possible explanation for differences in HPV positive rates may be the different LBC technologies used. Table 3.1.3 shows the overall rates for each technology, suggesting a higher positive rate with ThinPrep[®] LBC (68.7%) than with BD SurePath[™] LBC (61.6%). This difference remained after adjustment for age group and initial cytology result. However LBC technology is confounded by site, and it was therefore not possible to determine whether this difference was due to the technology used or to other differences between the sites. In the only site to use both technologies, there was no significant difference in positive rates between the two technologies.

Table 3.1.4 shows the HPV positive rate in women whose test was due to a first routine call, compared to women whose test was due to a routine recall. The positive rate was significantly higher ($p < 0.001$) in women who are attending for a first routine call (72.0%) than in women attending for routine recall (65.7%). However women attending for a first routine call will be younger, and when the rates were standardised for age there was very little difference (routine call; 65.1% and routine recall; 67.7%).

3.2 RLU Values

Table 3.2.1 gives the RLU values for women who were HPV positive by initial cytology result and age group, ranging from 2-4347 RLU/Co. The percentage of RLU values that were >100 RLU/Co decreased with increasing age, as did the mean and median RLU value. The mean and median RLU values were higher in women with initial mild dyskaryosis than in women with initial borderline dyskaryosis in all age groups. Using a cut off of 1.0 RLU would have resulted in an additional 504 (5%) women being referred to colposcopy (385 (5/9%) of women with borderline samples and 119 (3.4%) of those with mild dyskaryosis).

3.3 Attendance at colposcopy for HPV positive women

Follow up was available for at least six months for all HPV positive women at initial cytology. Of these 6470, 5838 (90.2%) attended colposcopy. The attendance rates by age group and initial cytology result are shown in table 3.3.1. There was a slight but significant increasing trend in attendance with increasing age ($p=0.02$), but no significant difference with initial cytology result. Rates of attendance ranged from 96.2% to 81.4% by site . The highest rate of non-attendance due to the patient opting for private care was 4.4%.

3.4 Result at colposcopy in HPV positive women

Table 3.4.1 shows the outcome at colposcopy in the 5838 HPV positive women who attended. The proportion of women who were negative at colposcopy, either due to a negative biopsy, negative cytology or a negative colposcopic assessment resulting in no biopsy being performed, was significantly higher in women with initial borderline cytology than in women with mild dyskaryosis, 59.9% and 48.3% respectively ($p<0.0001$). There were 166 women with positive (borderline changes or worse) cytology but a negative colposcopic examination; these women were considered to be negative for disease and no further information was collected.

There was no significant difference in the rate of CIN2+ by initial cytology result. In total 16.3% of women who attended colposcopy with borderline or mild dyskaryosis on the basis of a positive HPV test were found to have CIN2 or worse at histology; this included three cases of cervical cancer.

There was a highly significant decreasing trend in the proportion of colposcopies that were CIN2 or worse with increasing age group ($p<0.0001$). This was observed both in women with initial borderline and initial mild dyskaryosis.

3.5 Biopsy type at colposcopy

The colposcopy results by biopsy type, as provided by the sites, are presented in table 3.5.1. There were 298 colposcopies where the information on biopsy was not available or was coded as 'other'. Nearly nineteen percent of women who attended colposcopy were reported as not undergoing biopsy; however 16.0% of these women had a recorded diagnosis of CIN1. Almost 63% of all women who attended colposcopy underwent a diagnostic punch biopsy; 49.0% of these proved to be negative for CIN. A total of 196 women were reported as undergoing an excision biopsy; the majority of these (58.2%) were found to have CIN2 or worse, however almost 30% were negative for CIN. A further 442 women were known to have had a biopsy but the type was not specified.

Table 3.5.2 shows the type of biopsies performed by site. The percentage of women not undergoing biopsy ranged from 2.7% to 65.9%. The percentage of excision biopsies performed ranged from 5.6% to 0.9% , and the percentage of punch biopsies from 26.5% to 95%.

The percentage of women who underwent biopsy but were negative for disease ranged from 93.6%, to 13.0%.

3.6 Positive predictive value of a positive HPV test

The positive predictive value (PPV) of a positive HPV test for detecting high grade CIN was 6.1% for CIN3 or worse and 16.3% for CIN2 or worse (Table 3.6.1). The PPV for CIN3 or worse was slightly but significantly higher in women with initial borderline cytology than in women with initial mild dyskaryosis (6.7% vs. 5.4%; $p=0.034$); this was not observed for CIN2 or worse. The PPV decreases with increasing age group.

The PPV of HPV for detecting high grade disease varied by centre. Among women with borderline cytology the PPV for CIN2 or worse ranged from 9.3% to 21.5%, and the PPV for CIN3 or worse from 2.5% to 11.5%. In women with mild dyskaryosis the PPV for CIN2 or worse ranged from 9.1% to 33.0% in Sheffield, and that for CIN3 or worse ranged from 2.5% to 15.2%. (Table 3.6.2)

Standardising for age and for the ratio of borderline to mild tests did not reduce the difference in PPV between sites. The age and ratio standardised PPV of a positive HPV test for detection of high grade CIN for borderline cytology and mild dyskaryosis combined are presented for each site in table 3.6.3. The highest positive predictive values were still observed in those sites with the highest ratio of borderline to mild tests when standardised data was considered.

3.7 Subsequent management in women with CIN1 at colposcopy

A total of 1329 women were found to have CIN1 at colposcopy; according to the protocol these women could either be treated and undergo test of cure 6 months later as is the protocol for women with CIN2 or worse, or not be treated and simply undergo a repeat cytology 12 months after colposcopy.

Table 3.7.1 shows the subsequent management of women with CIN1; information was available for 36.0% of these women: 32.9% were not treated and returned for a repeat cytology at 12 months, 2.7% underwent treatment and attended for test of cure at 6 months. Attendance for further management did not appear to be associated with age or initial cytology result.

Although no information was available for the majority of women, 25.2% of those who had no further recorded management had less than 6 months follow up since their colposcopy and 73.6% had less than 12 months.

Tables 3.7.2 shows the subsequent management in women with CIN1 restricted to those who had at least 12 months follow up after colposcopy before the end of data collection. The rate of attendance was 68.4%, with the majority of women (64%) having repeat cytology and only 4% being treated. A large proportion of women who are not treated are having their repeat cytology before it is due at 12 months; the mean time between colposcopy and attendance at repeat cytology was 7.4 months and the median 6.7 months. Initial cytology result does not appear to be associated with subsequent attendance for repeat cytology.

For those women who did have repeat cytology the results are shown in table 3.7.4. Almost 40% of women had abnormal cytology, however only 3.4% had moderate dyskaryosis or worse.

SECTION 3- TABLES

Table 3.1.1 HPV positive rates by age group and initial cytology result

Table 3.1.2 HPV positive rates by site

Table 3.1.3 HPV positive rates by LBC technology

Table 3.1.4 HPV positive rates by reason for test

Table 3.2.1 RLU values in HPV positive women by initial cytology result and age group

Table 3.3.1 Attendance rates for colposcopy in HPV positive women

Table 3.4.1 Results at colposcopy in HPV positive women

Table 3.5.1 Results at colposcopy by biopsy type

Table 3.5.2 Biopsy type by centre

Table 3.6.1 Positive predictive value of a positive HPV test for detecting high grade CIN

Table 3.6.2 Positive predictive value of a positive HPV test for detecting high grade CIN by site

Table 3.6.3 Positive predictive value of a positive HPV test for detecting high grade CIN stratified by site and standardised for age and BL: Mild Ratio

Table 3.7.1 Subsequent management in women with CIN1

Table 3.7.2 Subsequent management in women with CIN1 who had at least 12 months to return for further management

Table 3.7.3 Outcome of 12 month cytology in women with untreated CIN1

Table 3.1.1 HPV positive rates by age group and initial cytology result

Age gp	Borderline		Mild		Total	
	Number of women	HPV+ n (%)	Number of women	HPV+ n (%)	Number of women	HPV+ n (%)
25-34	3121	2144 (68.7)	2203	1964 (89.2)	5324	4108 (77.2)
35-49	2783	1165 (41.9)	1129	869 (77.0)	3912	2034 (52.0)
50-64	603	187 (31.0)	212	141 (66.5)	815	328 (40.2)
Total	6507	3496 (53.7)	3544	2974 (83.9)	10051	6470 (64.4)

Table 3.1.2 HPV positive rates by Site

Site	Crude HPV+ rate	Age-Standardised HPV+ rate*	Ratio of BL:Mild tests
A	68.4%	70.3%	1 : 0.5
B	52.1%	54.1%	1 : 0.8
C	57.7%	58.4%	1 : 0.6
D	74.3%	74.0%	1 : 0.8
E	74.1%	73.3%	1 : 0.3
F	75.9%	76.5%	1 : 0.2

* standardised to the whole Sentinel sites study population age distribution

Table 3.1.3 HPV positive rates by LBC technology

		ThinPrep® LBC		BD SurePath™ LBC	
		Number of women	HPV+ n (%)	Number of women	HPV+ n (%)
BL	25-34	1932	1405 (72.7)	778	515 (66.2)
	35-49	1630	747 (45.8)	719	308 (42.8)
	50-64	341	118 (34.6)	164	51 (31.1)
	Total	3903	2270 (58.2)	1660	874 (52.6)
Mild	25-34	1374	1263 (91.9)	529	446 (84.1)
	35-49	693	565 (81.5)	293	214 (72.8)
	50-64	112	83 (74.1)	73	44 (60.3)
	Total	2179	1911 (87.7)	895	703 (78.5)
TOTAL		6082	4181 (68.7)	2555	1578 (61.6)

* Data on LBC technology were unavailable for 1411 women (BL n=943, Mild n=468)

Table 3.1.4 HPV positive rates by reason for test

		Routine call		Routine recall	
		Number of women	HPV+ n (%)	Number of women	HPV+ n (%)
BL	25-34	825	611 (74.1)	1385	976 (70.5)
	35-49	332	147 (44.3)	1590	756 (47.5)
	50-64	79	21 (26.6)	341	123 (36.1)
	Total	1236	779 (63.0)	3316	1855 (55.9)
Mild	25-34	568	518 (91.2)	964	857 (88.9)
	35-49	129	101 (78.3)	668	532 (79.6)
	50-64	29	15 (51.7)	119	86 (72.3)
	Total	726	634 (87.3)	1751	1475 (84.2)
TOTAL		1962	1413 (72.0)	5067	3330 (65.7)

*3022 women were not recorded as having a test as a result of routine call or routine recall (Annual cytology tests n=14, Clinically indicated n=29, Opportunistic n=151, Other n=652, Previous abnormal n=120, Previous inadequate n=81, Previous treatment n=13, Reason unknown n=1962)

Table 3.2.1 RLU value in HPV positive women by initial cytology result and age group

		RLU VALUE								
		2.0 - 4.9 n (%)	5.0 - 9.9 n (%)	10.0 - 49.9 n (%)	50.0 - 99.9 n (%)	>100 n (%)	nk n (%)	TOTAL n (%)	Mean	Median
BL	25-34	94 (4.4)	90 (4.2)	277 (12.9)	155 (7.2)	1144 (53.4)	384 (17.9)	2144 (100.0)	522	238
	35-49	72 (6.2)	52 (4.5)	171 (14.7)	94 (8.1)	584 (50.1)	192 (16.5)	1165 (100.0)	471	187
	50-64	15 (8.0)	9 (4.8)	33 (17.6)	13 (7.0)	83 (44.4)	34 (18.2)	187 (100.0)	457	147
Mild	25-34	46 (2.3)	38 (1.9)	121 (6.2)	88 (4.5)	1208 (61.5)	463 (23.6)	1964 (100.0)	901	749
	35-49	31 (3.6)	14 (1.6)	65 (7.5)	42 (4.8)	552 (63.5)	165 (19.0)	869 (100.0)	849	641
	50-64	2 (1.4)	4 (2.8)	14 (9.9)	3 (2.1)	88 (62.4)	30 (21.3)	141 (100.0)	823	678
TOTAL		260 (4.0)	207 (3.2)	681 (10.5)	395 (6.1)	3659 (56.6)	1268 (19.6)	6470 (100.0)	671	384

* RLU values for 1268 HPV positive women were unavailable

Table 3.3.1 Attendance rates for colposcopy in HPV positive women

		Number HPV+ women	Attended Colposcopy n (%)
Borderline	25-34	2144	1929 (90.0)
	35-49	1165	1061 (91.1)
	50-64	187	171 (91.4)
	Total	3496	3161 (90.4)
Mild	25-34	1964	1750 (89.1)
	35-49	869	797 (91.7)
	50-64	141	130 (92.2)
	Total	2974	2677 (90.0)
TOTAL		6470	5838 (90.2)

Table 3.4.1 Results at colposcopy

		Inadequate/ unknown/ other n (%)	Negative n (%)	Positive Cytology n (%)	CIN1 n (%)	CIN2 n (%)	CIN3 n (%)	Cancer n (%)	Total n (%)
BL	25-34	64 (3.3)	1091 (56.6)	45 (2.3)	394 (20.4)	193 (10.0)	139 (7.2)	3 (0.2)	1929 (100.0)
	35-49	30 (2.8)	679 (64.0)	26 (2.5)	173 (16.3)	88 (8.3)	65 (6.1)	0 (0.0)	1061 (100.0)
	50-64	8 (4.7)	124 (72.5)	3 (1.8)	27 (15.8)	4 (2.3)	5 (2.9)	0 (0.0)	171 (100.0)
	Total	102 (3.2)	1894 (59.9)	74 (2.3)	594 (18.8)	285 (9.0)	209 (6.6)	3 (0.1)	3161 (100.0)
MILD	25-34	71 (4.1)	821 (46.9)	62 (3.5)	468 (26.7)	217 (12.4)	111 (6.3)	0 (0.0)	1750 (100.0)
	35-49	27 (3.4)	392 (49.2)	25 (3.1)	236 (29.6)	87 (10.9)	30 (3.8)	0 (0.0)	797 (100.0)
	50-64	3 (2.3)	80 (61.5)	5 (3.8)	31 (23.8)	8 (6.2)	3 (2.3)	0 (0.0)	130 (100.0)
	Total	101 (3.8)	1293 (48.3)	92 (3.4)	735 (27.5)	312 (11.7)	144 (5.4)	0 (0.0)	2677 (100.0)
Total		203 (3.5)	3187 (54.6)	166 (2.8)	1329 (22.8)	597 (10.2)	353 (6.0)	3 (0.1)	5838 (100.0)

Table 3.5.1 Colposcopy outcome by biopsy type

	nk/inad/other	No biopsy	Liquid based cytology	Biopsy (unspecified)	Punch biopsy	Excision biopsy	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
nk/inad/other	81 (27.2)	1 (0.1)	2 (1.1)	44 (10.0)	74 (2.0)	1 (0.5)	203 (3.5)
Negative	196 (65.8)	917 (83.9)	175 (98.3)	231 (52.3)	1778 (49.0)	56 (28.6)	3353 (57.4)
CIN1	19 (6.4)	175 (16.0)	1 (0.6)	108 (24.4)	1001 (27.6)	25 (12.8)	1329 (22.8)
CIN2+	2 (0.7)	0 (0.0)	0 (0.0)	59 (13.3)	778 (21.4)	114 (58.2)	953 (16.3)
Total	298 (100.0)	1093 (100.0)	178 (100.0)	442 (100.0)	3631 (100.0)	196 (100.0)	5838 (100.0)

Table 3.5.2 Biopsy type by site

	nk/inad/other	No biopsy	LBC	Biopsy (unspecified)	Punch biopsy	Excision biopsy	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
A	1 (0.1)	21 (2.7)	1 (0.1)	0 (0.0)	745 (95.0)	16 (2.0)	784 (100.0)
B	26 (5.3)	326 (65.9)	0 (0.0)	0 (0.0)	131 (26.5)	12 (2.4)	495 (100.0)
C	188 (9.0)	270 (13.0)	161 (7.7)	423 (20.3)	924 (44.4)	116 (5.6)	2082 (100.0)
D	76 (9.6)	90 (11.3)	6 (0.8)	2 (0.3)	613 (77.1)	8 (1.0)	795 (100.0)
E	3 (0.3)	248 (21.5)	10 (0.9)	17 (1.5)	836 (72.5)	39 (3.4)	1153 (100.0)
F	4 (0.8)	138 (26.1)	0 (0.0)	0 (0.0)	382 (72.2)	5 (0.9)	529 (100.0)
Total	298 (5.1)	1093 (18.7)	178 (3.0)	442 (7.6)	3631 (62.2)	196 (3.4)	5838 (100.0)

Table 3.6.1 Positive predictive value of a positive HPV test for detecting high grade CIN

		PPV (CIN2+)	PPV (CIN3+)
BL	25-34	17.4% (335/1929)	7.4% (142/1929)
	35-49	14.4% (153/1061)	6.1% (65/1061)
	50-64	5.3% (9/171)	2.9% (5/171)
	Total	15.7% (497/3161)	6.7% (212/3161)
Mild	25-34	18.7% (328/1750)	6.3% (111/1750)
	35-49	14.7% (117/797)	3.8% (30/797)
	50-64	8.5% (11/130)	2.3% (3/130)
	Total	17.0% (456/2677)	5.4% (144/2677)
TOTAL		16.3% (953/5838)	6.1% (356/5838)

Table 3.6.2 Positive predictive value of a positive HPV test for detecting high grade CIN by site

		PPV (CIN2+)	PPV (CIN3+)
A	BL	16.5% (71/430)	7.4% (32/430)
	Mild	21.8% (77/354)	7.6% (27/354)
B	BL	11.2% (20/178)	6.2% (11/178)
	Mild	9.1% (29/317)	3.5% (11/317)
C	BL	11.6% (113/978)	5.0% (49/978)
	Mild	15.9% (176/1104)	4.8% (53/1104)
D	BL	9.3% (33/355)	2.5% (9/355)
	Mild	10.9% (48/440)	2.5% (11/440)
E	BL	21.5% (173/803)	7.8% (63/803)
	Mild	25.4% (89/350)	7.1% (25/350)
F	BL	20.9% (87/417)	11.5% (48/417)
	Mild	33.0% (37/112)	15.2% (17/112)

Table 3.6.3 Positive predictive value of a positive HPV test for detecting high grade CIN stratified by site and standardised for age and BL: Mild Ratio

	PPV (CIN2+)	PPV (CIN3+)
A	16.9%	6.9%
B	8.3%	3.9%
C	12.0%	4.4%
D	9.3%	2.5%
E	20.4%	6.5%
F	24.7%	12.3%

Table 3.7.1 Subsequent management in women with CIN1

		Cytology at 12 months	Treatment and ToC at 6 months	DNA- reason known	DNA- reason unknown	Total
		n (%)	n (%)	n (%)	n (%)	n (%)
BL	25-34	130 (33.0)	9 (2.3)	2 (0.5)	253 (64.2)	394 (100.0)
	35-49	66 (38.2)	9 (5.2)	2 (1.2)	96 (55.5)	173 (100.0)
	50-64	7 (25.9)	1 (3.7)	0 (0.0)	19 (70.4)	27 (100.0)
Mild	25-34	141 (30.1)	9 (1.9)	2 (0.4)	316 (67.5)	468 (100.0)
	35-49	82 (34.7)	7 (3.0)	0 (0.0)	147 (62.3)	236 (100.0)
	50-64	11 (35.5)	1 (3.2)	0 (0.0)	19 (61.3)	31 (100.0)
Total		437 (32.9)	36 (2.7)	6 (0.5)	850 (64.0)	1329 (100.0)

Table 3.7.2 Subsequent management in women with CIN1 who had at least 12 months to return for further management

	Cytology at 12 months	Treatment and ToC at 6 months	DNA- reason known	DNA- reason unknown	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
BL	113 (63.5)	9 (5.1)	1 (0.6)	55 (30.9)	178 (100.0)
Mild	113 (65.3)	5 (2.9)	2 (1.2)	53 (30.6)	173 (100.0)

Total	226 (64.4)	14 (4.0)	3 (0.9)	108 (30.8)	351 (100.0)
--------------	-------------------	-----------------	----------------	-------------------	--------------------

Table 3.7.3 Outcome of 12 month cytology in women with untreated CIN1

		Negative n (%)	Borderline n (%)	Mild n (%)	Moderate n (%)	Severe+ n (%)	Inadequate n (%)	Total n (%)
BL	25-34	74 (56.9)	23 (17.7)	21 (16.2)	3 (2.3)	2 (1.5)	7 (5.4)	130 (100.0)
	35-49	50 (75.8)	8 (12.1)	6 (9.1)	0 (0.0)	1 (1.5)	1 (1.5)	66 (100.0)
	50-64	4 (57.1)	3 (42.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (100.0)
Mild	25-34	76 (53.9)	24 (17.0)	33 (23.4)	5 (3.5)	1 (0.7)	2 (1.4)	141 (100.0)
	35-49	43 (52.4)	21 (25.6)	14 (17.1)	2 (2.4)	0 (0.0)	2 (2.4)	82 (100.0)
	50-64	5 (45.5)	0 (0.0)	5 (45.5)	1 (9.1)	0 (0.0)	0 (0.0)	11 (100.0)
Total		252 (57.7)	79 (18.1)	79 (18.1)	11 (2.5)	4 (0.9)	12 (2.7)	437 (100.0)

4. EPIDEMIOLOGICAL EVALUATION OF HPV AS A TEST OF CURE AFTER TREATMENT

This section presents the results of the evaluation of HPV as a test of cure. This includes women who were triaged to colposcopy on the basis of a positive HPV test and were diagnosed with CIN1 or worse. It also includes women who followed the non-triage route; these were women who were previously treated for CIN1, 2 or 3 following high grade cytology or persistent low grade cytology and who underwent a test of cure 6 months after treatment. These two groups are evaluated separately unless stated.

Triage Route

4.1 Attendance for test of cure

Test of cure cytology and HPV test, if required were due 6 months after treatment for CIN. The attendance rates for test of cure by grade were 37.2% and 44.8% for women treated for CIN 2 and 3 respectively (the three women diagnosed with cervical cancer were excluded from this step). Only 2.7% of women with CIN1 attended for test of cure, as the majority had not be treated; of those 473 women with a known management after CIN1 was diagnosed, 36 (7.6%) were treated and 437 (92.4%) had a repeat cytology. For women with CIN2 or worse the low attendance is in part due to lack of follow up; 23.6% of women with CIN2 and 21.5% of women with CIN3 had had less than 6 months follow up since their colposcopy, so had not had sufficient time to return for further management. Due to time constraints data collection for this analysis finished before all women had completed the protocol, however these women will stay in the protocol and their outcomes will be recorded by the sites for possible analysis in the future.

Among women with at least 6 months follow up after treatment, 41.4% (190/456) of those treated for CIN2 and 49.1% (136/277) of those treated for CIN3 attended test of cure.

4.2 Test of cure outcome

A total of 416 women attended test of cure cytology; 65 (15.6%) of these had abnormal cytology and a further 42 (10.1%) were cytologically normal but tested positive for HPV. Therefore in total 25.7% of women who were tested 'failed' the test of cure. The failure rate was highest in women previously treated for CIN1; 47.2% compared to 27.0% and 19.0% failure in women treated for CIN2 and CIN3 respectively.

4.3 Subsequent colposcopy in women who 'failed' test of cure

The attendance rate for colposcopy after test of cure 'failure' was 38.5% in women who failed due to abnormal cytology, and 38.1% in those who failed due to a positive HPV test. Again lack of follow up will explain the low estimated attendance.

Table 4.3.1 summarises the final outcome in those women who did attend colposcopy; 65.9% of all women were negative at biopsy or were considered colposcopically normal and did not undergo biopsy and 12.2% had CIN2 or worse detected. This is lower than the rate of CIN2 or worse at original colposcopy (16.3%) but not significantly so. The rate of CIN2 or worse is higher among women referred to colposcopy with abnormal cytology compared to those referred with a positive HPV test; 16.0% and 6.3% respectively, but the difference is not significant.

Non-Triage Route

4.4 Test of Cure outcome

Table 4.4.1 describes the cytology and histology history by age group of the 3203 women who attended for non-triage test of cure. The majority of women (60.5%) had previously been treated for CIN3. However within the group who were referred to colposcopy with persistent low grade cytology more women had been treated for CIN2 than CIN3. The majority (59.2%) of women entering the study were aged 25-34. Women in this age group were significantly more likely to have been treated for CIN3 than women aged 35-49 ($p<0.0001$) and women aged 50-64 ($p=0.0001$).

Table 4.4.2 gives the outcomes at test of cure in these 3203 women. Overall 18.3% of women 'failed' test of cure; either due to abnormal cytology (6.2%) or a positive HPV test (12.1%). There is a highly significant trend ($p<0.0001$) of increasing failure rate with decreasing grade of CIN treated (excluding cervical cancer due to the small numbers involved). The failure rates by age group were 18.0%, 17.3% and 28.3% in women aged 25-34, 35-49 and 50-64 respectively.

4.5 Subsequent colposcopy in women who 'failed' test of cure

Overall 73.7% of women who failed test of cure attended for a subsequent colposcopy. Table 4.5.1 shows that the highest rate of attendance was in women treated for CIN1 (77.9%) and in women aged 35-49 (80.7%). Women who failed due to abnormal cytology were significantly more likely to attend for colposcopy than women who failed due to a positive HPV test; 87.8% compared to 66.6% ($p<0.0001$).

Table 4.5.2 shows the result at subsequent colposcopy in women who attended. The overall rate of high grade CIN is 6.9%; however the rate of CIN2 or worse is only 2.7% in women who were positive for HPV, but 13.3% in women with abnormal cytology. There were also significantly more colposcopies that were classed as negative in the HPV positive group; 83.4% compared to 53.8% ($p<0.0001$). The rates of CIN2 or worse by age group were 6.6%, 7.5% and 6.4% for the age groups 25-34, 35-49 and 50-64 respectively.

4.6 Positive predictive value of HPV test of cure for detection high grade CIN

The positive predictive value of a positive HPV test in women with negative cytology for predicting the presence of residual high grade CIN after treatment is 0.4% for CIN3 or worse compared to 8.1% in women with an abnormal cytology (Table 4.6.1). For CIN2 or worse the PPVs are 2.7% and 13.3% respectively.

SECTION 4- TABLES

Table 4.1.1 Six month test of cure in women with CIN1 or worse at colposcopy

Table 4.3.1 Colposcopy result after test of cure failure

Table 4.4.1 Non-triage test of cure

Table 4.4.2 Non-triage test of cure; Outcome of test of cure

Table 4.5.1 Non-triage Test of Cure; Attendance for colposcopy after test of cure
Failure

Table 4.5.2 Non-triage test of cure; Outcome after test of cure failure

Table 4.6.1 Positive predictive value of HPV infection for predicting high grade
CIN after treatment

Table 4.1.1 Six month Test of Cure in women with CIN1 or worse at Colposcopy

	Test of cure	Test of Cure		
		abnormal cytology	HPV+	Total 'failed' test of cure
		n (%)	n (%)	n (%)
CIN1	36	6 (16.7)	11 (30.6)	17 (47.2)
CIN2	222	40 (18.0)	20 (9.0)	60 (27.0)
CIN3	158	19 (12.0)	11 (7.0)	30 (19.0)
TOTAL	416	65 (15.6)	42 (10.1)	107 (25.7)

Table 4.3.1 Colposcopy result after test of cure failure

		Negative n (%)	Positive Cytology n (%)	CIN1 n (%)	CIN2 n (%)	CIN3 n (%)	Total n (%)
Abnormal cytology	25-34	11 (61.1)	1 (5.6)	4 (22.2)	1 (5.6)	1 (5.6)	18 (100.0)
	35-49	3 (42.9)	1 (14.3)	1 (14.3)	0 (0.0)	2 (28.6)	7 (100.0)
	Total	14 (56.0)	2 (8.0)	5 (20.0)	1 (4.0)	3 (12.0)	25 (100.0)
HPV+	25-34	10 (76.9)	0 (0.0)	2 (15.4)	1 (7.7)	0 (0.0)	13 (100.0)
	35-49	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
	Total	13 (81.3)	0 (0.0)	2 (12.5)	1 (6.3)	0 (0.0)	16 (100.0)
Total		27 (65.9)	2 (4.9)	7 (17.1)	2 (4.9)	3 (7.3)	41 (100.0)

* No women aged 50-64 attended colposcopy after test of cure failure

Table 4.4.1 Non-Triage Test of Cure

Previous Histology		CIN1 n (%)	CIN2 n (%)	CIN3 n (%)	Cancer n (%)	Total n (%)
High Grade	25-34	41 (2.9)	352 (25.1)	1010 (72.0)	0 (0.0)	1403 (100.0)
	35-49	61 (7.5)	220 (26.9)	533 (65.2)	3 (0.4)	817 (100.0)
	50-64	12 (10.3)	33 (28.4)	71 (61.2)	0 (0.0)	116 (100.0)
Persistent	25-34	82 (16.6)	202 (40.9)	210 (42.5)	0 (0.0)	494 (100.0)

Low Grade	35-49	95 (29.4)	122 (37.8)	105 (32.5)	1 (0.3)	323 (100.0)
	50-64	28 (56.0)	12 (24.0)	10 (20.0)	0 (0.0)	50 (100.0)
TOTAL		319(10.0)	941 (29.4)	1939 (60.5)	4 (0.1)	3203 (100.0)

Table 4.4.2 Outcome of Non-triage test of cure

Previously treated histology	Non triage Test of cure	Test of Cure		
		abnormal cytology n (%)	HPV+ n (%)	Total 'failed' test of cure n (%)
CIN1	319	39 (12.2)	47 (14.7)	86 (27.0)
CIN2	941	55 (5.8)	115 (12.2)	170 (18.1)
CIN3	1939	102 (5.3)	227 (11.7)	330 (17.0)
Cancer	4	1 (25.0)	0 (0.0)	1 (25.0)
TOTAL	3203	197 (6.2)	389 (12.1)	586 (18.3)

Table 4.5.1 Non-triage Test of Cure; Attendance for colposcopy after test of cure failure

		Failed Test of Cure	Attended Colposcopy n (%)
CIN1	25-34	33	19 (57.6)
	35-49	40	36 (90.0)
	50-64	13	12 (92.3)
	Total	86	67 (77.9)
CIN2	25-34	92	63 (68.5)
	35-49	69	51 (73.9)
	50-64	9	3 (33.3)
	Total	170	117 (68.8)
CIN3+	25-34	217	160 (73.7)
	35-49	88	72 (81.8)
	50-64	25	16 (64.0)
	Total	330	248 (75.2)
TOTAL		586	432 (73.7)

Table 4.5.2 Non-triage test of cure; Outcome after test of cure failure

Reason for failure		Colposcopy Outcome							
		Inadequate/ unknown/ other	Negative	Positive Cytology	CIN1	CIN2	CIN3	Cancer	Total
Cytology abnormal		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	25-34	11 (13.8)	45 (56.3)	10 (12.5)	4 (5.0)	3 (3.8)	7 (8.8)	0 (0.0)	80 (100.0)
	35-49	7 (9.2)	42 (55.3)	11 (14.5)	5 (6.6)	6 (7.9)	5 (6.6)	0 (0.0)	76 (100.0)
	50-64	3 (17.6)	6 (35.3)	3 (17.6)	3 (17.6)	0 (0.0)	2 (11.8)	0 (0.0)	17 (100.0)
	Total	21 (12.1)	93 (53.8)	24 (13.9)	12 (6.9)	9 (5.2)	14 (8.1)	0 (0.0)	173 (100.0)
HPV+	25-34	7 (4.3)	137 (84.6)	6 (3.7)	6 (3.7)	6 (3.7)	0 (0.0)	0 (0.0)	162 (100.0)
	35-49	4 (4.8)	69 (83.1)	4 (4.8)	5 (6.0)	0 (0.0)	1 (1.2)	0 (0.0)	83 (100.0)
	50-64	2 (14.3)	10 (71.4)	2 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (100.0)
	Total	13 (5.0)	216 (83.4)	12 (4.6)	11 (4.2)	6 (2.3)	1 (0.4)	0 (0.0)	259 (100.0)
Total		34 (7.9)	309 (71.5)	36 (8.3)	23 (5.3)	15 (3.5)	15 (3.5)	0 (0.0)	432 (100.0)

Table 4.6.1 Positive predictive value of HPV infection for predicting high grade CIN after treatment

	PPV (CIN3+)		PPV (CIN2+)	
	Abnormal Cytology	8.1%	(14/173)	13.3%
Normal Cytology and HPV+	0.4%	(1/259)	2.7%	(7/259)

5 KOILOCYTES AND BORDERLINE GLANDULAR TESTS

Recently the BSCC indicated that they wished to move samples which contain koilocytes from the borderline cytology category into mild dyskaryosis, and to alter the management of women with borderline abnormalities in glandular cells so that they were subject to HPV triage or referred immediately to colposcopy.

Only two sites were able to provide data on presence of koilocytes. There were 250 women with borderline cytology who had the presence of koilocytes recorded. The HPV positive rate was 76.8%; at every age group it was significantly higher than that observed in all women with borderline dyskaryosis (83.7%, 72.5% and 55.6% in women aged 25-34, 35-49 and 50-64 respectively). The mean and median RLU values are also higher. However the HPV positive rates in women with koilocytes are still significantly lower than those in women classed as having mild dyskaryosis, as are the median and mean RLU values. Therefore it is possible that moving women with koilocytes into the mild category could decrease the HPV positive rate in among women with borderline dyskaryosis, but also decrease the rate in women with mild dyskaryosis. The rate of CIN2 or worse in women with borderline dyskaryosis and koilocytes identified was significantly lower than in all women with borderline dyskaryosis at 7.7%.

However, only 2 centres are represented in this analysis, and in one there was no significant difference in the rate of HPV positives in borderline women with and without koilocytes. 75.3% and 76.1% respectively ($p=0.56$). In the other site the HPV positive rate was higher in women with koilocytes; (87.1% compared to 57.4%) but this was based on only 31 women.

There were only 17 women identified who had borderline abnormalities in glandular cells. The rate of HPV positivity was 70.6% among these women. This is slightly higher than that observed in all women with borderline changes, however it is based on very small numbers and the confidence intervals indicate the true percentage could lie anywhere between 44 and 90%. Therefore we can not draw any conclusions about how the different management of this group would affect clinical or cost effectiveness. The rate of detection of high grade CIN in these women was 33.3% which is higher than that observed in the whole population, but again these numbers are too small to be useful.

6 ECONOMIC EVALUATION

6.1 Methods

The aim of the economic analysis was to quantify the costs and effects, and the cost effectiveness of adopting HPV testing as implemented in the Sentinel sites study. Specific objectives of the economic analysis were as follows:

- measuring costs for HPV testing
- reviewing utility and patient preference for HPV testing
- cost-effectiveness of HPV triage
- cost-effectiveness of HPV test of cure

Measuring cost

The cost analysis was carried out from the NHS perspective. All costs refer to 2009; where required costs were adjusted using the Hospital and Community Health Service (HCHS) pay and price index¹². Equipment and consumable costs associated with HPV testing were estimated from the cost incurred at laboratories and in consultation with suppliers. Unit costs of staff time were derived from observational studies, mostly undertaken specifically for the Sentinel sites study, and existing tariffs and contracts, as well as from published sources. Table 1 reports the staff unit costs used in the analysis.

Salary costs were then attributed for each activity based on the mid-scale point for the corresponding band in the Agenda for Change salary structure¹³. Salary costs included qualifications and NHS employers' costs (that is, the employer's national insurance contribution plus 14 percent of salary for employer's contribution to superannuation). Cost per minute of staff time is given in Table 1.

Three separate categories of cost were considered:

- (a) training and implementation costs
- (b) cost of administration, identifying samples/specimen reception and transport
- (c) cost of HPV testing.

Table 6.1: Cost per minute for laboratory staff

Staff	Cost/min (£)	Source
MLA	£0.19	13,12
MLA3	£0.20	13, 12
Cytoscreener	£0.24	13,12
BMS	£0.29	13,12
Senior BMS	£0.42	13,12
Pathologist	£1.36	14
Advanced practitioner	£1.10	13,12
Consultant	£2.82	13,12

Training and implementation

A cost questionnaire was devised to assess the potential additional costs of HPV testing for the Sentinel site laboratories not performing HPV testing on site (see Appendix 1). The questionnaire assessed the following components of cost:

- training costs for cytology laboratory staff
- training cost for staff taking cytology samples
- cost of transporting LBC samples for HPV testing
- administrative and other costs – IT system charge

A cost questionnaire was also devised to identify the cost incurred at HPV testing laboratories which included: staff training costs, equipment and consumable costs (see Appendix 2). The questionnaire identified the costs of training current staff for performing HPV testing.

Cost of administration, identifying samples/specimen reception and transport

When calculating administration, sample identification/reception and transport costs we compared two alternative service delivery models for HPV testing:

- ‘hub and spoke model’, and
- integrated HPV/cytology laboratory.

In the ‘hub and spoke model’, cytology laboratories without HPV testing facilities on site, considered as spokes, would identify LBC vials requiring HPV tests and arrange to transport them to a separate laboratory for processing, considered as a hub. In contrast, with the integrated HPV laboratory both cytology and HPV testing facilities are provided at the same laboratory.

In the ‘hub and spoke’ model costs of administration and identifying/specimen reception are incurred in both spoke laboratories (i.e. cytology laboratories) and hub laboratories (HPV laboratories). Record sheets were developed to record the amount of staff activity related to HPV testing in spoke laboratories. Timings were recorded for the following activities:

- identifying cytological samples for HPV testing
- packing samples for transporting to the HPV laboratory
- updating clinical records
- administration time

The slides were then transported to HPV laboratories. The costs of spoke-to-hub transport of vials for processing were estimated from the average journey transport costs and numbers of samples transported. Record sheets were developed to record the amount of staff activity related to HPV testing in a hub laboratory. The costs of following staff activities were identified.

- specimen reception and unpacking
- updating clinical records
- administration time

One HPV laboratory was an ‘integrated cytology laboratory’ (Bristol) where HPV testing has been started ‘de novo’ in an existing cytology laboratory. In the integrated ‘HPV/cytology’ laboratory scenario the following costs were included and there is no requirement for transportation costs:

- identifying cytological samples for HPV testing
- updating clinical records
- administration time

Data from the record sheet survey were used to determine the duration of time required and grades of staff undertaking each activity and costed as described above.

Costs of performing HPV tests

The cost of HPV testing includes: equipment, consumables, and staff costs. Equipment and consumables for HPV testing were based on the QIAGEN High-Risk HPV HC2 DNA Test as used in the Sentinel sites study. A range of further HPV test alternatives are currently on the market and further ongoing evaluation is being undertaken on these tests. Potential differences could include: differences in price and batch sizes required to achieve efficiency and avoid waste.

Costs were based on a manual preparation system as used in Sentinel sites laboratories undertaking the HPV testing. Again further equipment is available from the manufacturer with elements of automation, but this was not assessed within this evaluation. Costing of HPV equipment/consumables was based on five year contract lease prices and the modelled throughput of different sized HPV laboratories. To maintain confidentiality over indicative prices, we present prices in combination with the staff costs associated with preparing HPV tests. Indicative prices for equipment and maintenance were obtained from QIAGEN.

A questionnaire was devised and sent to the laboratories undertaking HPV testing to assess the costs of other equipment not provided by QIAGEN to identify the consumable and staff time involved. (See Appendix). Information was also obtained on the costs of HPV consumables and staff processing time depending on the number of tests being processed in each batch. Costs of HPV testing are highly dependent on the batch size being processed at one time, and costs are therefore presented for batches of different sizes.

During the Sentinel sites study HPV tests were processed on a twice weekly basis. An important consideration for HPV testing is that it can be integrated within the overall cytology pathway to meet government targets of women receiving their results within 14 days of a smear being taken. Within the implementation project, some cytology laboratories were also taking part in the lean improvement

project and successfully managed to achieve a 14 day turn-around time including sending smears for HPV testing.

An alternative option would be that HPV processing was conducted on a daily basis to further improve turn-around times; however this would only be economically efficient if there was a sufficient quantity of tests. We assessed the volume of HPV tests for each of these roll-out by combining the data from the epidemiological evaluation on the volume of HPV tests (for both HPV triage of mild and borderlines and HPV test of cure) with estimates of the numbers of routine cytology tests from the Korner Returns; the national screening programmes statistical returns (KC-61).

The following different sized laboratories were considered:

- HPV testing in individual cytology laboratories (35,000 cytology slides per year)
- HPV testing across cytology laboratories (100,000 cytology slides per year)
- 2 HPV laboratories at Strategic Health Authority level
- 1 HPV laboratory at Strategic Health Authority level
- 1 National HPV processing laboratory

6.1.2 Utility and patient preference for HPV triage/HPV test of cure

We reviewed the literature to summarise the current evidence comparing women's preferences/valuations between immediate follow-up and repeat testing of minor abnormalities. Eliciting and understanding patient preferences is an important part of clinical decision making. Understanding women's preferences for alternative screening methods would help designing appropriate screening policy which will maximise women's participation in the relevant programme.

We conducted a systematic review of the literature using the online bibliographic information service PubMed database from 1966 to 24th March 2009. The aim was to identify empirical studies evaluating women's preference/valuations of alternative management pathways for low grade cervical screening abnormalities.

We used a number of search terms to identify studies evaluating women with low grade cytological abnormalities: (ASCUS or atypical squamous cells or low grade or borderline or mild*) and (pap or smear or cytolog* or cervical). This search was then combined with search terms to identify studies that assessed either preferences, values or utility (pref* or valu* or willingness-to-pay or WTP or util*). In addition, we searched the bibliographic references of these studies to identify further studies. We included all English language studies that collected primary data.

6.1.3 Cost-effectiveness of HPV triage for mild and borderline results

Previous cost-effectiveness modelling work has shown that HPV triage is likely to be highly cost-effective compared with repeat cytology when used in combination with liquid based cytology^{8 15}. However, a limitation in both these modelling exercises was the predicted increase in colposcopy workload generated by HPV triage compared to repeat screening. Both these analyses are based on modelled assumptions about the probabilities of repeat cytology tests and colposcopy referral. Because of these limitations it was not possible to update the estimates of cost-effectiveness in the present study.

Table 6.2 provides a summary of the costs included in the workload and cost-effectiveness modelling exercise. Costs of cytology tests were based on updated data from the original pilot site report¹⁶, HPV testing as detailed later in the report. Other costs were taken from the published literature. Where required costs were updated using the hospital and community health services index.

Table 6.2: Cost data: 2009 prices

Item	Cost (£)	Source
LBC test cost in laboratory*	£7.19	HPV/LBC Pilot site ¹⁶ cost inflated using HCHS index ¹²
HPV test reflex costs*	£12.83 [†]	HPV Sentinel sites study
Consult cost – GP/nurse visit in community	£17.56	Includes administration and smear taking time. Based on 80% of smear taken by practice nurses ¹⁶
Outpatient visit	71.34	¹⁷ cost inflated using HCHS index ¹²
Colposcopy	210	Payment by results. Department of Health, 2009.
Punch Biopsy	75.92	¹⁵ and inflated using HCHS index ¹²
Cone biopsy	345.18	¹⁷
Treatment ‡:		
- CIN 1	439.61	Average cost per event, ¹⁷
- CIN 2/3	617.97	Average treatment cost of CIN2 & CIN3 from ¹⁷
Cancer		
-Stage I	2785	
-Stage II	4448	
-Stage III	12,562	Average cost per event ¹⁷)
-Stage IV	12,777	

* Including storage, transport, laboratory, sample media, vials

† 12.73 was used in the cost-effectiveness assessment for HPV used after treatment for CIN

‡ Averaged for proportion receiving LEEP or cone by CIN grade

6.1.4 Modelling HPV testing for cure following the treatment of CIN

To date the cost-effectiveness of using HPV testing as a ‘test of cure’ for the treatment of CIN has not been evaluated in a UK setting. Implementing such a policy has potential health benefits and utility

implications for women, as well as resource implications for HPV testing, cytology and colposcopy services. The objective of this part of the study was to compare the cost-effectiveness of two alternative HPV test of cure protocols with current practice.

As described previously in the report, in the HPV Sentinel sites study, HPV testing (using Hybrid Capture II) was used in the management of women following treatment for cervical intraepithelial neoplasia (CIN) where cytology results were negative at 6 month follow-up. Clinical evidence suggests that women who are cytology negative and HPV negative at 6 months after treatment for CIN can safely be returned to 3-year recall¹⁸.

Currently HPV testing is not routinely undertaken as part of the NHS cervical screening programme. Instead guidelines recommend annual recall for all women treated for CIN 2/3 for at least 10 years after treatment. For women treated for low grade disease, cytology follow-up is recommended at 6, 12 and 24 months - if all results are negative then return to routine recall¹ - otherwise annual recall is recommended¹⁹.

When modelling current colposcopy practice, an important consideration is that there are differences in policies across clinics. In 2004, a national survey of colposcopy clinics highlighted significant variations in colposcopy practice²⁰. For example, there are differences in the management of CIN1, both in the number of follow-up visits prior to treatment, and whether treatment is undertaken at all. However, for the purposes of the current modelling exercise, consideration is restricted to the comparative downstream costs and benefits for treated women. We assumed that post treatment follow-up protocols adhere to national guidelines.

The model simulated a cohort of women that have been treated for CIN (1-3). The cohort simulated was structured in terms of age and disease distribution to be consistent with that seen at the HPV Sentinel sites. Costs and effects were examined in all women over a 10 year time horizon. This time horizon was chosen to capture downstream management costs for all of the alternative post-treatment management pathways, as current management for women treated for CIN involves annual cytological follow-up for a period of at least 10 years.

Outcome measures

The outcomes of interest are defined as: cumulative case numbers of histologically confirmed CIN 2+ over 10 years, cumulative case numbers of histologically confirmed CIN 3+ over 10 years, and 10 year costs (discounted). These outcomes were examined in the full treated cohort of women. Quality of life measures (QALYs) were not used, as utility weight data have not been reported for a post-treatment population.

Management pathways

Three alternate post-treatment management pathways were simulated:

1. Current practice (Non HPV test of cure arm)

- Women treated for low grade disease have 6, 12 and 24 month cytology - if all results are negative then return to routine recall,² otherwise continue with annual management.
- Women treated for CIN 2/3 have annual follow-up for 10 years following treatment.

2. Post-treatment management as implemented in the HPV Sentinel sites

¹ 3 yearly for women between the age of 25 and 50, 5 yearly for women over 50 (note women over 65 will still complete the protocol)

² 3 yearly for women between the age of 25 and 50, 5 yearly for women over 50 (note women over 65 will still complete the protocol)

- Women testing cytology and HPV negative at 6 months post-treatment return to routine recall.
- Women testing HPV positive or borderline dyskaryosis or worse on cytology at 6 months undergo colposcopy.
- Women who are treated for CIN 2+ during the 10 year period are followed up after this subsequent treatment with cytology and HPV testing at 6 months. Subsequent management is as if this was their first treatment.

3. *Post-treatment management as implemented in Kitchener et al, BJOG 2008*¹⁸

- Women testing cytology and HPV negative at both 6 months and 12 months post-treatment have repeat cytology only at 24 months post-treatment. If they have negative cytology at 24 months post-treatment, they return to routine recall.

Women testing HPV positive or cytology borderline dyskaryosis or worse at any stage undergo colposcopy. Women who are treated for CIN 2+ during the 10 year period are followed up after this subsequent treatment with cytology and HPV testing at 6 and 12 months, and cytology only at 24 months. All management is as if this was their first treatment.

Model structure

The model uses a Markov modelling approach. Separate health states and transitions between them are modelled to reflect the underlying natural history of HPV and CIN. The definition of model health states is shown in Appendix Table 10.1. A second natural history is used in women treated for histologically confirmed CIN 2/3, to reflect their higher risk of recurrent disease. All natural history transitions (average risk and post-treatment) were based on prior work^{21 22 23}. The model was parameterised based on a literature review on the probability of post-treatment recurrence and the efficacy of HPV testing after CIN 2/3 treatment to predict recurrent disease. We used a fitting approach to ensure that the model correctly predicts key outcomes which can be compared to clinical data, for example, the probability of abnormal cytology at 6 and 12 months, and histological detection of disease recurrence at 6, 12, 24 and 72 months.

Overlaid on these natural history models are models of screening and post-treatment management pathways, and test characteristics of LBC, HC-II, and colposcopy. Management pathways in the model map the follow up surveillance pathways outlined above. The associated costs of these events are mapped and tracking variables are used to identify women progressing to CIN 2 and CIN 3/invasive cancer. The model uses a 6 month time-step, in order to capture screening and follow-up events which occur at 6 month intervals.

The cohort of women simulated was structured such that their age and disease distribution at the time of treatment was consistent with that seen at the HPV Sentinel sites. Thus, 10% of women were originally treated for CIN 1, 32% for CIN 2, and 58% for CIN 3. 63% of the women were aged 25-34 years at the time of initial treatment, 35% were aged 35-49 years, and 2% were aged 50-64 years. Alternative population structures were considered during sensitivity analysis. The populations are described in detail in an Appendix.

Compliance estimates were based on data from the NHS cervical screening programme in England²⁴, and a study involving comparable management in a post-treatment cohort¹⁸. Further analysis assessed the impact of assuming perfect compliance with all follow-up visits, colposcopy, treatment, and routine screening.

Sensitivity analysis

A one- way sensitivity analysis was performed to determine how sensitive the findings of this modelled analysis were to various model assumptions. The following assumptions were varied over a feasible range of possible values:

1. Age composition of the cohort of women treated for CIN
2. The proportion of women who were treated for each grade of CIN (1-3)
3. The cost of collecting follow-up test samples (i.e. whether this was done in the community or by a specialist in a hospital setting)
4. Test characteristics of Hybrid Capture II
5. Test characteristics of LBC (accuracy and inadequate rate)
6. Test characteristics of colposcopy

Limitations of the model

The model produces predictions for detected CIN 2+ and CIN 3+ recurrence for each post-treatment management strategy, over the first 10 years post-treatment. Although model predictions were made over a 10-year time horizon, they are extrapolations based on data from studies with shorter follow-up periods, and are therefore not guarantees of safety. Follow-up data from prospective studies of HPV as a test of cure do not yet extend to 10 years. A Swedish case-control study found that HPV testing at 6 and/or 12 months post-treatment of CIN 2/3 had low sensitivity for predicting recurrence which occurred more than two years after initial treatment ²⁵.

Furthermore, there is little evidence for safety beyond the 10-year time horizon. There is evidence that women previously treated for CIN 3 remain at an increased risk of cancer for at least 25 years post-treatment ²⁶. The model predicted costs and effects under the three management pathways specified. We did not examine all possible management pathways. The modelled outputs should always be interpreted as predictions based only on short-term follow-up data, rather than upon direct clinical evidence over the longer term.

6.2 Economic Results

6.2.1. Training and implementation

Training of staff in cytology laboratories handling samples for HPV testing offsite

A range of staff were involved with training for handling HPV tests that would then be sent for external processing offsite (see Appendix Table 5 for details). Training topics covered for identifying samples included following protocols and correct placement of slide numbers. Staff involved with packing cytology samples were given training on: explaining protocols, quality control steps to ensure correct totals were included, and health and safety guidance. Training on updating records with HPV results included: verbal explanation of protocols, instruction in the use of databases, and quality control-steps to reduce transposition errors. Overall training times for cytology staff varied from about an hour to half a day, and were mainly provided in-house.

Training of staff taking cytology samples

The number of staff that received training about HPV testing provided by the cytology laboratories varied across the sites, from 52 to 212 (further details of the smear taker training are provided in the Appendix). Where fewer staff were trained, alternatives were used such as cascading information to

staff and distributing HPV information packs. An alternative model was to organise two formal presentations for all smear takers lasting three hours, and then to visit each GP practice where there had been no representation at either event. The cost of smear taker training provision varied between no direct costs (apart from staff time) to £2500. It is anticipated that these training costs should be covered locally as part of routine training updates for smear takers.

Training of staff in laboratories undertaking HPV testing

Details of the provision of training in laboratories undertaking HPV testing are provided in the Appendix (tables 4-6). In the laboratory where HPV testing was already being undertaken training of staff on HPV testing was carried out through in-house training. In the integrated HPV/cytology laboratory training was carried out by both QIAGEN and in-house staff. QIAGEN provided training on running assays and occasional troubleshooting matters. In-house training was also provided for staff on receiving and preparing samples, and reporting results.

Administrative and other costs for laboratories

There were some information technology (IT) system changes in all the cytology laboratories for changing codes, setting up the system, and establishing electronic links for the Exeter system (See Appendix table 7). Each site had to ensure that new result codes matched with the final result letters sent to women. On average it took three days to perform IT changes. Most sites did not incur any financial costs (beyond in house staff time), other than one site which spent £2250 on IT system changes.

6.2.2. Cost of administration, identifying samples/specimen reception and transport

Cost of staff time in cytology laboratories with HPV testing provided offsite

Record sheets were developed to record the amount of staff activity related to HPV testing at four cytology laboratories without HPV testing (Norwich, Northwick Park, Liverpool and Sheffield). Timings were recorded for the following activities: identifying cytological samples for HPV testing, packing samples for transporting to the HPV laboratory, updating clinical records and administration time. These data show very similar results across three of the sites, with the total staff time per HPV sample at between 5-6 minutes (Table 6.3). In one site (C) the staff time was much higher due to a much higher estimate of administration time. Again the cost of staff time per HPV sample was similar across three of the sites £1.77-£1.85, but at site C it was higher (£4.45) due to the higher estimate of staff administration time. The average additional cost for: administration, identifying samples, packing, and updating clinical records of HPV samples were £2.66 (CI £1.72-3.61).

Table 6.4: Time per HPV sample in cytology laboratories with HPV testing offsite in minutes – mean (95% CI)

Activity	A	B	C	D
Identify sample	2.10 (0.84, 3.36)	0.75 (0.55, 0.95)	0.73 (0.46, 1.00)	1.17 (0.75, 1.60)
Packing	1.60 (0.94, 2.26)	0.96 (0.86, 1.06)	3.03 (2.16, 3.91)	1.11 (0.23, 1.99)
Update records	1.27 (0.65, 1.89)	1.52 (1.31, 1.72)	3.72 (3.01, 4.43)	2.91 (2.14, 3.67)
Admin time	0.47 (0.12, 0.82)	2.19 (1.95, 2.43)	5.63 (2.75, 8.51)	0 (0, 0)
Total	5.44 (2.55, 8.34)	5.41 (4.66, 6.17)	13.11 (8.37, 17.85)	5.19 (3.12, 7.26)

Table 6.5: Cost per HPV sample in cytology laboratories with HPV testing offsite £ – mean (95% CI)

Activity	A	B	C	D
Identify sample	£0.76 (£0.30, £1.22)	£0.27 (£0.20, £0.34)	£0.26 (£0.17, £0.34)	£0.43 (£0.27, £0.58)
Packing	£0.46 (£0.27, £0.65)	£0.28 (£0.25, £0.31)	£0.88 (£0.62, £1.13)	£0.32 (£0.07, £0.57)
Update records	£0.51 (£0.26, £0.76)	£0.61 (£0.53, £0.69)	£1.50 (£1.21, £1.78)	£1.17 (£0.86, £1.48)
Admin time	£0.18 (£0.05, £0.32)	£0.84 (£0.75, £0.94)	£2.07 (£1.06, £3.28)	£0 (£0, £0)
Total	£1.92 (£0.88, £2.95)	£2.00 (£1.72, £2.28)	£4.81 (£3.06, £6.56)	£1.91 (£1.20, £2.63)

Cost of transporting samples for HPV testing

The cost of transporting LBC samples for HPV testing per journey is reported in the Appendix Table 8. Each centre sent samples for HPV testing to HPV laboratories twice a week. The average number of samples sent per journey was 14 (range 10-18). The cost per journey across centres varied from £5 to £50. Sentinel sites study A and D were located at relatively close proximities to HPV laboratories (just under 50 KM) compared with sites B and C (150-300 KM). Sites A and D both incurred similar delivery costs – transporting up to 12 samples at a price of £5 per box and a larger box cost £25 to transport up to 40 samples. Sites B and C generally sent samples in a larger box that could contain 40 or more HPV samples at a cost of between £40- £50 per box. The average transport costs per sample across the two sites located approximately 50 KM away were £0.44 (range £0.38 to £0.50). For those sites located further from the HPV processing laboratory (150-300KM), average transport costs per sample were higher at £2.76 (range £2.20-£3.33).

Cost of administration, identifying samples/specimen reception in HPV laboratories

The costs of administration (reporting results) and identifying samples/specimen reception in HPV laboratories were estimated from a record sheet survey. For this exercise, the objective was to compare the costs of two alternative delivery options: ‘hub and spoke’ versus integrated

‘cytology/HPV’ testing laboratory. In the cytology laboratory which was performing HPV testing on site (Bristol), only the times for identifying samples for HPV testing and administration for reporting the results were recorded. At the other separate HPV processing centre (Manchester), we considered the costs of identifying samples and administration including reporting results back to the cytology laboratory.

Table 6.6: Time per sample in minutes in HPV laboratories – mean (95% CI)

Activity	Separate HPV testing centre	Integrated cytology/HPV laboratory
Specimen reception (separate) Identifying samples (integrated)	1.03 (0.93, 1.13)	3.28 (2.05, 4.52)
Reporting results administration	0.84 (0.43, 1.26)	0.96 (0.63, 1.29)
Total	1.87 (1.36, 2.39)	4.24 (2.68, 5.81)

Table 6.7: Cost per sample in HPV laboratories – mean (95% CI)

Activity	Separate HPV testing centre	Integrated cytology/HPV laboratory
Specimen reception (separate) Identifying samples (integrated)	£0.24 (£0.22, £0.26)	- £0.76 (£0.48, £1.05)
Reporting results administration	£0.24 (£0.12, £0.36)	£0.28 (£0.18, £0.37)
Total	£0.48 (£0.34, £0.62)	£1.04 (£0.66, £1.42)

**Cost comparison between ‘hub and spoke model’ and ‘integrated cytology/HPV laboratory’:
administration, identifying samples/specimen reception and transport**

Table 6.8: Cost per sample – mean (95% CI) [range]

Activity	HPV lab receiving samples externally	Integrated HPV/cytology laboratory
Cost of staff time in cytology laboratory	£2.66 (£1.72, £3.61)	NA
Transport cost		NA
Transport distance - (150-300KM), Transport distance – (>50KM)	£2.76 [£2.20, £3.33] £0.44 [£0.38, £0.50]	
Specimen reception (separate)	£0.24 (£0.22, £0.26)	-
Identifying samples (integrated)	-	£0.76 (£0.48, £1.05)
Reporting results	£0.24 (£0.12, £0.36)	£0.28 (£0.18, £0.37)
Total		
Transport distance - (150-300KM)	£5.90 (£5.20, £7.56)	
Transport distance – (>50KM)	£3.58 (£3.38, £4.73)	
		£1.04 (£0.66, £1.42)

The ‘integrated HPV/Cytology’ laboratory leads to lower total costs for administration, identifying samples/specimen reception and transport than that of ‘hub-and-spoke’ model. With the ‘hub-and-spoke’ model these costs ranged from £3.58 - £5.90 per sample depending on the transportation distance, the equivalent costs for the integrated laboratory were £1.04. The integrated laboratory does not incur any cost for transporting samples.

The ‘hub-and-spoke’ model leads to higher costs than integrated HPV/Cytology laboratory. When the distance between cytology and HPV laboratory is more than 150KM the difference in cost per sample is £4.86 and when cytology laboratory was within 50KM, the additional cost compared to an integrated laboratory was £2.54 per sample.

6.2.3. Costs of performing HPV testing

During the Sentinel sites study the QIAGEN High-Risk HPV HC2 DNA test was used. Each kit has 96 wells including 8 wells that are used as controls for each batch. There are economies of scale related to running full batches including: the need for 8 controls even with smaller batches, use of slightly more consumable costs per test, higher average equipment costs and increases in staff time per test. Table 6.9 presents the total HPV testing costs for different size batches. Alternative HPV tests that can potentially run smaller batch sizes are also being evaluated which could potentially be more cost efficient. The cost assessment includes confidential prices from QIAGEN; these are only indicative and would be dependent on the volume of test ordered and contract negotiation.

Table 6.9: Cost per HPV test for alternative batch sizes (£)

	HPV batch size			
	88	66	44	22
HPV test cost	£12.83	£14.03	£16.42	£20.97

The cost of HPV test varies from £12.83 to £20.97 depending on batch size. The cost of an HPV test includes the cost of equipment, consumables, maintenance, and staff time. These costs all increase

when running smaller batches. It is most cost efficient to perform HPV testing at full batch capacity (88 samples per batch) £12.83 per test. However, the marginal increase in cost for running 66 samples compared to 88 is only an additional £1.20 per test which could potentially be offset by decreased transport costs if HPV testing is operating in laboratories that do not have sufficient capacity to run full batches. The volume of tests for HPV processing centres serving different sized cytology laboratories were estimated from workload data from one laboratory for 2010. Options included:

- HPV testing in individual cytology laboratories (35,000 cytology slides per year)
- HPV testing across cytology laboratories (100,000 cytology slides per year)
- 2 HPV laboratories at Strategic Health Authority level
- 1 HPV laboratory at Strategic Health Authority level
- 1 National HPV processing laboratory

Table 6.10 shows that running HPV testing daily in the first three options would be inefficient as there would be unused capacity. Running daily HPV testing with full batches would only be possible if an HPV processing centre serves cytology laboratories reading over 0.3 million slides per year. An alternative would be to have one National laboratory. However, transport costs are higher over longer distances. A further potential advantage of larger laboratories is the use of further technologies that increase automation of the HPV testing process which have not been evaluated within this project.

Based on running HPV tests twice a week it is possible to run full batches with two HPV testing centres per Strategic Health Authority (SHA) This may also be a cost-effective option if transport costs are reduced, especially where the SHA covers a large geographic area.

However it should be noted that the HPV testing workload figures will vary from year to year according to the protocols being followed.

Table 6.10: Volume of HPV tests for alternative roll-out options

	Number of HPV testing centres required	Annual cytology workload	Annual HPV testing workload	Tests per batch if testing twice a week	Tests per batch if testing everyday
Each cytology laboratory	103	35000	2514	24	10
Sharing across several laboratories	36	100000	7183	69	28
2 HPV testing laboratories per SHA	20	180000	12390	124	50
1 HPV testing centre per SHA	10	360000	25859	249	100
1 National laboratory	1	3600000	258291	2486	995

6.2.4 Utility and patient preference for HPV triage/HPV test of cure

In total eight studies were identified (see Appendix Table 8) which met our selection criteria. Two studies used willingness to pay, five measured utility scores, and two identified general preferences. Two UK based studies^{27 28} measured women's strength of preference by using willingness to pay (WTP) as an outcome. Phillips et al²⁷, conducted a WTP experiment with 1141 women attending for routine GP consultations in the UK to assess women's preferences between repeat cytology or HPV tests as a triage. Over 81% of respondents would be willing to pay for a cytology test – of these 72% would be willing to pay extra for HPV triage. On average adding HPV triage to a cytology programme increased the valuation by 47%. The study also examined whether providing additional information about HPV testing affects valuation of HPV testing. Provision of information and corresponding valuation was undertaken in two stages. First, participants were informed that HPV testing is more accurate, can distinguish between women whose abnormalities will disappear and those whose abnormalities will not, and that HPV testing leads to early resolution of uncertainty and thereby appropriate follow up. Respondents were then asked about their valuation. Second, some less favourable information regarding HPV testing was supplied including the fact that HPV is a sexually transmitted infection. The respondents were asked if they would like to revise their earlier valuation. The results showed that providing favourable and less favourable information regarding HPV testing had very little impact on valuation of participants (83% of the participants have not revised their earlier valuation).

Whynes et al²⁸ conducted an exit survey on women who participated in TOMBOLA (Trial of Management of Borderline and Other Low Grade Abnormal cytology tests), a randomised controlled trial comparing alternative management strategies (cytological surveillance or immediate colposcopy) following the detection of low-grade cytological abnormalities. In the exit survey 190 women completed a questionnaire eliciting opinions on their management, contingent valuation of management methods and preferences. Although each women in TOMBOLA had been randomized to one (repeat cytology or immediate colposcopy) method, but at recruitment each woman has been informed about the both screening options. The study asked each woman to speculate how her CV might have differed had she been allocated to the alternative management method. A high proportion of women are satisfied with the method to which they had been randomized. The results show that women were equally satisfied with their management method and regarded them as equally valuable. Similarly no significant differences were found in preference ratings and mean CV of alternative

methods. Mean CVs for alternative methods were £397.9 for colposcopy and £514.3 surveillance. The difference in mean was statistically insignificant. When invited to value the alternative management method, about three-quarter of the women in each group has not revised their original CV. Within the minority of women who chose to revise their CV, significantly more women in surveillance group placed a higher value on the alternative than did those experiencing colposcopy. Four studies measured women's utility scores. Two of these studies collected data from women actually experiencing different management pathways whilst the others were based on hypothetical scenarios.

Maissi et al²⁹ assessed women's state anxiety, distress, concern and quality of life when they have had an HPV test following a borderline or mildly dyskaryotic smear test results. The study population was recruited from two centres participated in English pilot study of HPV testing. Participants included two groups of women receiving abnormal cytology results: tested for HPV and found to be (a) HPV positive and (b) HPV negative, and two groups not tested for HPV - those receiving (c) abnormal cytology results, and (d) normal cytology results. There were no significant differences in utility between these four groups of respondents. Melnikow et al³⁰ evaluated preference of ethnically diverse women for the management of a low-grade abnormal cytology results with early colposcopy or observation with repeat tests. The study sample was recruited from 5 five family planning clinics in Northern California's Central Valley. Overall utility for early colposcopy was found slightly higher than that of repeat cytology, but the mean difference in utilities were small.

Two studies used an experimental approach to try and assess process utility associated with hypothetical scenarios of the overall care pathway. Howard et al³¹ interviewed 67 women who were eligible for screening in which women's preference for alternative managements of atypical squamous cells of undermined significance (ASCUS) on cytology (repeat test compared with immediate HPV test) was evaluated and process utility was measured using a two-stage SG method. Overall they found that HPV triage had lower process utility than cytology.

Birch et al.³² also tested the presence of process utility. Two approaches were compared - conservative follow up (watchful wait/repeat Pap smear) and aggressive follow up (early intervention with colposcopy). A total of 170 subjects were interviewed to identify their relative process utility given different hypothetical scenarios about the underlying pathology. The respondent's preferred conservative follow up approach where pathologies did not indicate the need for treatment, and where pathologies indicate the need for a procedure, subjects on average prefer aggressive follow up.

Two general preference studies conducted internationally were identified that addressed the choice between repeat cytology and HPV triage. Ferris et al³³ found that most women preferred a repeat pap smear to further evaluate an initial pap smear demonstrating ASCUS and colposcopy to evaluate a report of LSIL. In contrast, McCaffery et al³⁴ in another general preference study has found that most of the women (65%) prefer HPV triage, although a substantial minority (35%) preferred repeat cytology.

The majority of the studies indicate that women prefer HPV testing to repeat smear tests even though HPV testing may lead to some additional initial distress. The studies indicate that although there may be a negative emotional effect associated with positive HPV test results this is essentially short-term, it is not apparent beyond 6/12 month period. A few points need to be considered in generalising the result - (a) relative utility or preference between is dependent on both sequence of events leading to an outcome in each option and particular circumstances under consideration, (b) there may have some heterogeneity in the mean preference estimates. McCaffery et al³⁴ examined the predictors of preference for HPV testing. They have found that women who had children, had a previous abnormal Pap smear and who were more anxious about their abnormal result were more likely to choose HPV testing. The association with a previous abnormal Pap smear result is interesting and may reflect dissatisfaction with their previous management experience. In conclusion, evidence from the UK strongly suggests that overall HPV testing appears to be the preferred choice of women, but there are a minority of women who prefer repeat follow-up.

6.2.5 Cost-effectiveness of HPV as a ‘test of cure’ following CIN treatment

Modelling indicated that post-treatment management with HPV testing as in the HPV Sentinel sites study is likely to be cost saving compared to current practice over a ten year time horizon (Table 6.11). Post-treatment management with HPV testing according to the protocol used in Kitchener et al¹⁴ was predicted to be more expensive than current practice. Both HPV testing management protocols were predicted to result in fewer cases of detected CIN 3+ and CIN 2+ over this time period (Table 6.11, Figure 6.1).

In both cases, more re-treatments were required, due to the higher test positivity associated with adding HPV testing at the 6 month visit. As shown in Table 6.11, re-treatments associated with post-treatment HPV testing are considerably lower from 12 months on. The number of cytology tests is also reduced for both HPV testing strategies. Total colposcopies over ten years are reduced by HPV testing as implemented in the HPV Sentinel sites, but increased by HPV testing as implemented in Kitchener et al¹⁸.

Exploration of disease reduction in HPV testing scenarios

In order to explore whether the predicted reduction in CIN 3+ and CIN 2+ reflected a true reduction in underlying disease, or missed cases, we used the model to estimate detected CIN 1. As CIN 1 is re-treated in all scenarios, detection and treatment of CIN 1 may avert some subsequent cases of CIN 2+. Cases of CIN 1 detected at intermediate time points are shown in Table 6.12. More histological CIN 1 is detected in the HPV testing scenarios. As histological CIN 1 is always re-treated in the model, it is possible that this prevents the some instances of CIN 2+ recurrence; however the discrepancy in CIN 2+ and CIN 3+ is greater than could be explained by additional CIN 1 detection.

To further explore the predicted lower disease detection under HPV testing scenarios, we used the model to estimate the true underlying prevalence of CIN 3+ at each time point over the 10 years (Figure 6.1). If the underlying CIN 3+ prevalence predicted by the model was higher for the HPV testing strategies at 10 years than for current practice, the lower number of detected cases would be a reflection of missed cases. Alternatively, if the underlying CIN 3+ prevalence predicted by the model was lower for the HPV testing strategies at 10 years than for current practice, the lower number of detected cases would be a reflection of reduced disease. We found that predictions for both the most effective strategy in terms of lowest CIN 3+ prevalence at 10 years, and the magnitude of underlying CIN 3+ prevalence over time, were sensitive to assumptions regarding compliance with follow-up visits.

For the first two years after initial treatment, prevalence of CIN 3+ is predicted to be lower in the scenarios where HPV testing is used, regardless of the assumptions made about compliance. This is because the higher sensitivity of combined testing is predicted to result in the removal or prevention of more CIN 3+ cases, via treatment. By 10 years, however, the assumptions regarding compliance made a difference to the relative performance of the management strategies, and hence whether the reduction in detected cases predicted for the HPV testing strategies is likely to represent missed or prevented cases. In the baseline model, where some loss to follow-up occurred based on routine data, current practice is predicted to have a higher underlying prevalence of CIN 3+ at 10 years than the HPV testing strategies. In a further scenario it was assumed that compliance was perfect for all strategies, in this case current practice performs very effectively and is predicted to have a lower underlying prevalence of CIN 3+ at 10 years than the HPV testing strategies. This indicates that the capacity of current practice to prevent CIN 3+ in the longer term is highly dependent on maintaining very high compliance with annual visits. While the overall effectiveness of HPV testing strategies is also reduced if compliance is not perfect, their effectiveness is far less dependent on compliance than the current strategy of annual follow-up. As true underlying CIN 3+ prevalence is unobservable in

practice, we could not directly verify model predictions. We did, however, compare model predictions for detected disease recurrence with published data^{18;35} and data from the HPV Sentinel sites, and found that they were consistent at the time-points for which comparable data were available (at 6, 12, 24, and 72 months). Details of model validation are presented in an Appendix.

As discussed above, and as shown in Figure 6.1, the HPV testing protocols have very similar outcomes in practice, in terms of true underlying CIN 3+ prevalence at 10 years. In Table 6.2 there appears to be a small difference between the two strategies, but this occurs because the cycle of three-yearly screening began (i.e. women were returned to routine screening) at different time periods after treatment. In the HPV Sentinel sites study protocol, this predominantly occurred at 6 months, while in the Kitchener protocol it predominantly occurred at 24 months. This means that screening and treatment occurs at slightly different time points for the different strategies. The small difference between the two HPV testing strategies at exactly 10 years is unlikely to reflect meaningful differences in outcomes.

While cases of CIN 3+ are predicted to decrease in strategies which use HPV testing to manage women post-treatment for CIN, this does not necessarily imply a reduction in cancer cases. The predicted reduction in CIN 3+ will be mostly driven by changes in CIN 3, as cancer is a much rarer outcome than CIN 3. Cancer rates were not explicitly examined

Sensitivity analysis

The main outcomes tested under sensitivity analysis were the cost per case of CIN 3+ detected, and the cost per true underlying CIN 3+ averted at 10 years compared to current practice. Results of the sensitivity analysis appear in Figure 6.2 and Figure 6.3.

Findings were most sensitive to assumptions regarding:

- The cost of collecting follow-up test samples (i.e. whether this was done in the community or by a specialist in a hospital setting)
- The proportion of treated women who were originally treated for CIN 1
- Test characteristics of Hybrid Capture II

Post-treatment management with HPV testing became more attractive when the cost of collecting follow-up test samples is higher (i.e. some or all are collected by a specialist rather than in the community). As more visits occur under the current management scenario, its total cost is increased by far more than that of the HPV testing scenarios.

Post-treatment management with HPV testing became less attractive when Hybrid Capture II had higher test positivity. Higher Hybrid Capture II positivity increases the costs associated with follow-up in the HPV testing scenarios, with little benefit (as baseline HC-II sensitivity for CIN 2+ was assumed to be high). HPV testing also became less attractive when the proportion of the cohort treated for CIN 1 was higher. This group was assumed to have a lower future risk for CIN 2+.

Findings were insensitive to assumptions regarding:

- Test characteristics of LBC (accuracy and inadequate rate)
- Test characteristics of colposcopy

HPV testing according to the Kitchener protocol was always more expensive over ten years than current practice. HPV testing as implemented in the HPV Sentinel sites study was generally less expensive than current practice. The single exception was when the overall HC-II positivity was assumed to be very high, which resulted in more treatments and higher costs, particularly at the 6-month follow-up visit.

Figure 6.1 Cumulative cases of histologically confirmed CIN 3+ detected, per 1,000 women treated

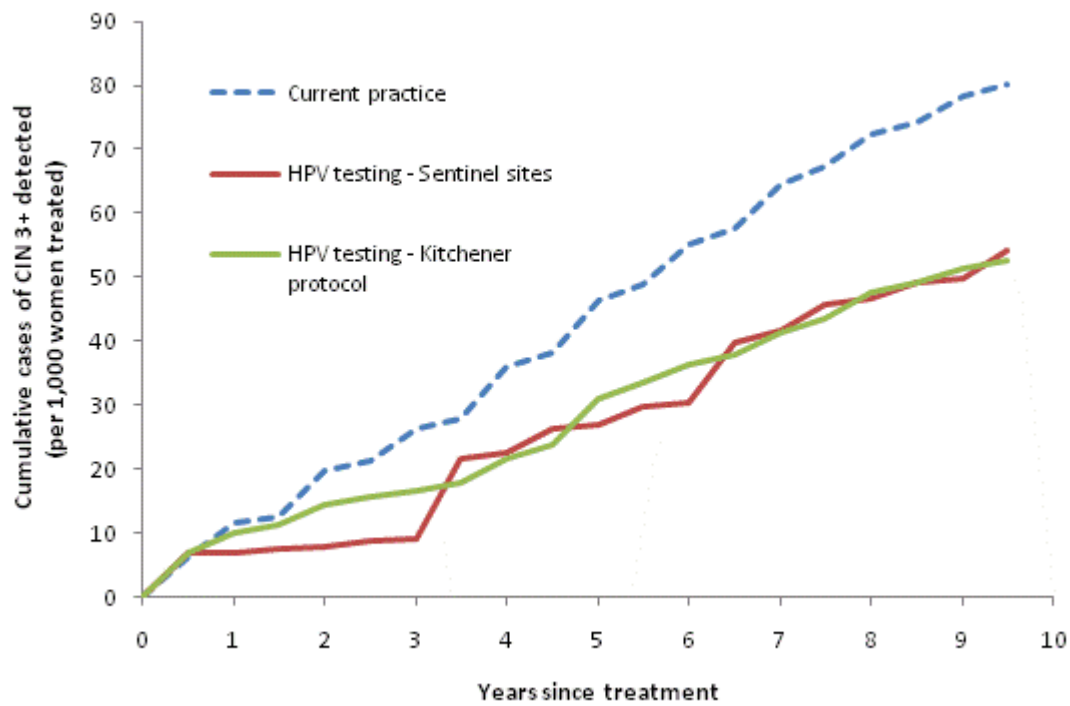


Table 6.11 Outcomes at 10 years (per 1,000 women treated)

Strategy	Current practice (annual visits)	HPV test of cure – Sentinel sites study protocol (6 month visit)	HPV test of cure –¹⁴ protocol (6,12,24 months visits)
Costs			
(discounted @ 3.5% pa)	£358,222	£348,834	£407,274
Total cases CIN 3+ detected †	80	54	53
Total cases CIN 2+ detected †	114	76	75
<i>At 6 months</i>	<i>10</i>	<i>11</i>	<i>11</i>
<i>By 12 months *</i>	<i>21</i>	<i>11</i>	<i>17</i>
<i>By 24 months *</i>	<i>41</i>	<i>12</i>	<i>21</i>
<i>By 5 years *</i>	<i>93</i>	<i>48</i>	<i>59</i>
Cost per case of CIN 3+ detected	£4,474	£6,446	£7,725
Underlying cases of CIN 3+ at 10 years	29.1	20.7	21.5
Underlying CIN 3+ cases averted compared to current practice	-	8.4	7.6
Cost per additional underlying CIN 3+ case averted at 10 years compared to current practice		-£1,120 (i.e. cost-saving)	£6,474
Resource use			
Colposcopies performed	406	368	447
Re-treatments‡ performed	217	272	275
<i>At 6 months</i>	<i>80</i>	<i>167</i>	<i>167</i>
<i>At 1 – 10 years</i>	<i>137</i>	<i>104</i>	<i>108</i>
Cytology tests performed	6,197	4,126	5,154
HPV tests performed	-	1,166	2,035

* Cumulative † Represents observed and detected cases, as distinct from true underlying cases of CIN 2+ and CIN 3+ in the population ‡ The number of re-treatments exceeds the number of detected high grades, as it includes treated low grades, and cone biopsies performed for reasons other than treatment (e.g. discordant cytology and colposcopy, unsatisfactory colposcopy following moderate or severe dyskaryosis cytology)

Table 6.12 CIN 1 outcomes at intermediate time points (per 1,000 women treated)

Strategy	Current practice (annual visits)	HPV test of cure – Sentinel sites study protocol (6 month visit)	HPV test of cure – Kitchener 2008 protocol ¹⁴ (6,12,24 months visits)
Cumulative cases CIN 1 detected			
At 6 months	14	24	24
By 12 months	17	24	25
By 24 months	18	24	26
By 5 years	19	25	26

Figure 6.2 Model-predicted underlying prevalence of CIN 3+ during the 10 years following initial treatment for three post-treatment management pathways

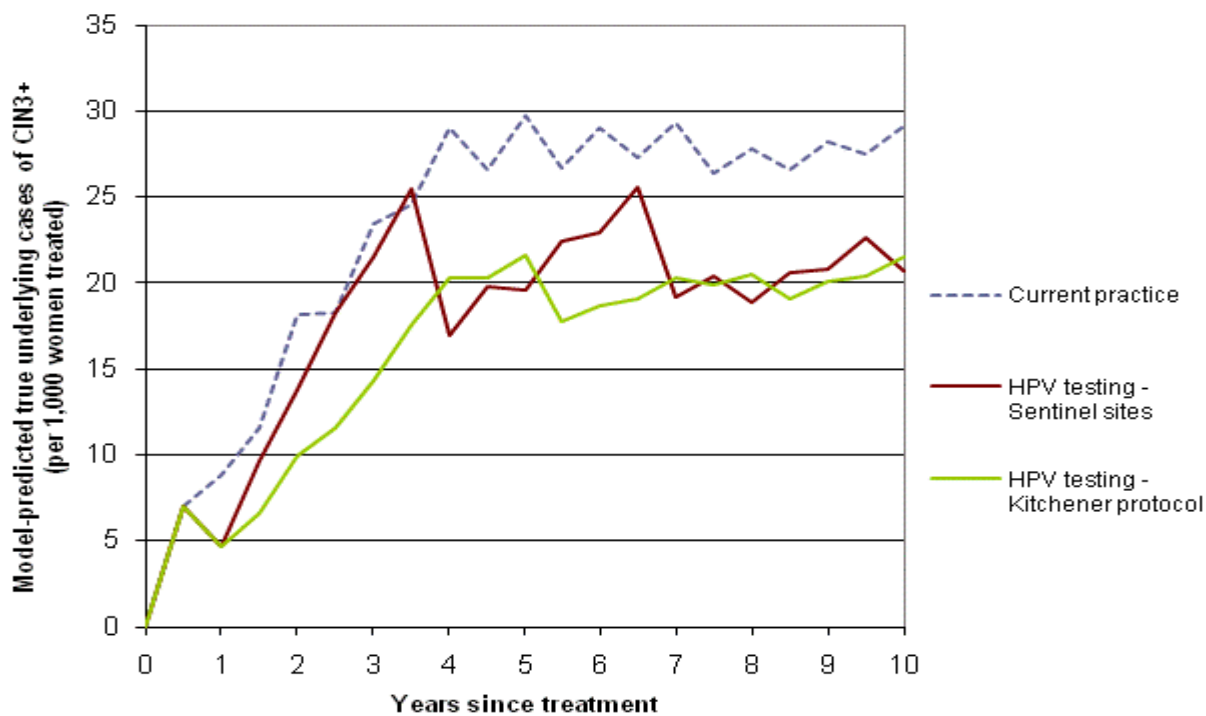
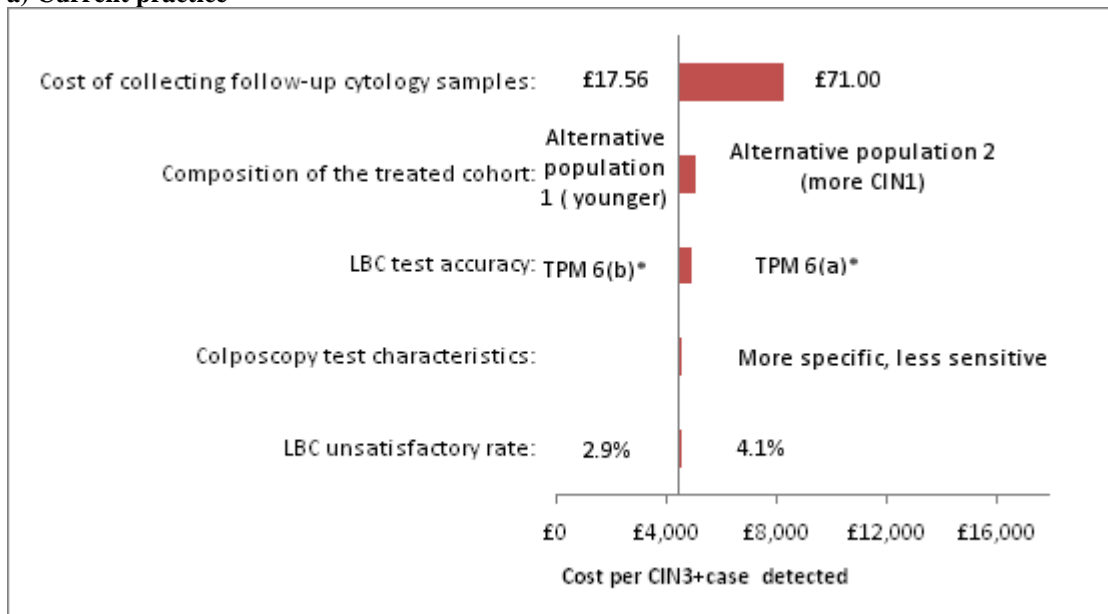


Figure 6.3 Impact of various model assumptions on the cost per CIN 3+ case detected

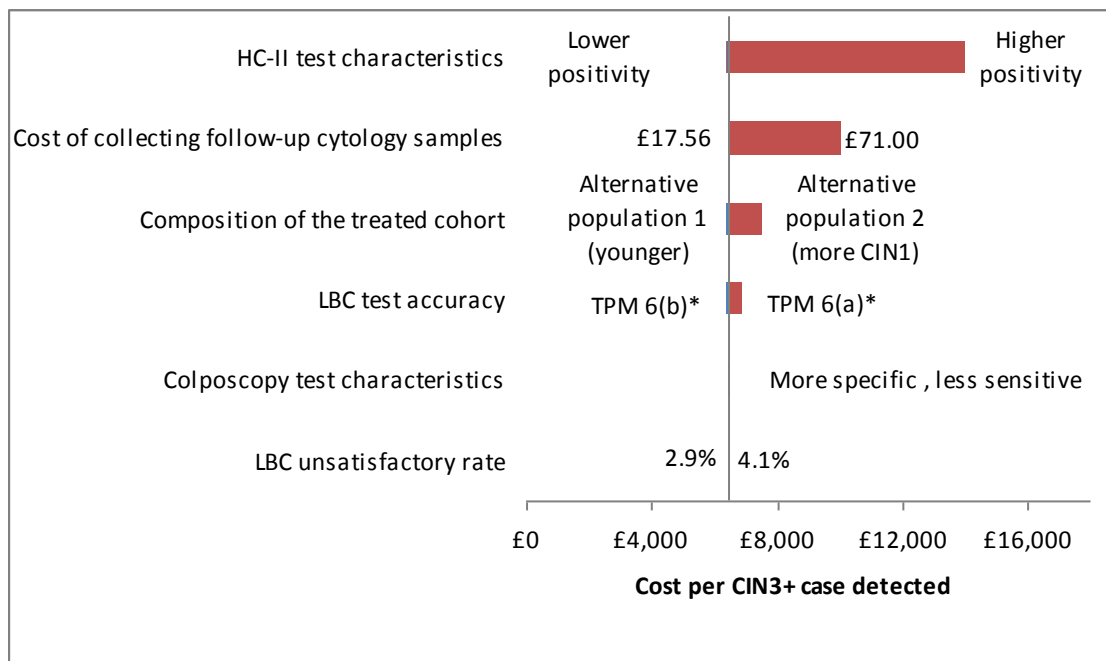
a) Current practice



Alternative populations are described in an Appendix.

* TPM 6(a) and TPM 6(b) refer to a set of test characteristics for LBC. They are described more fully in an Appendix

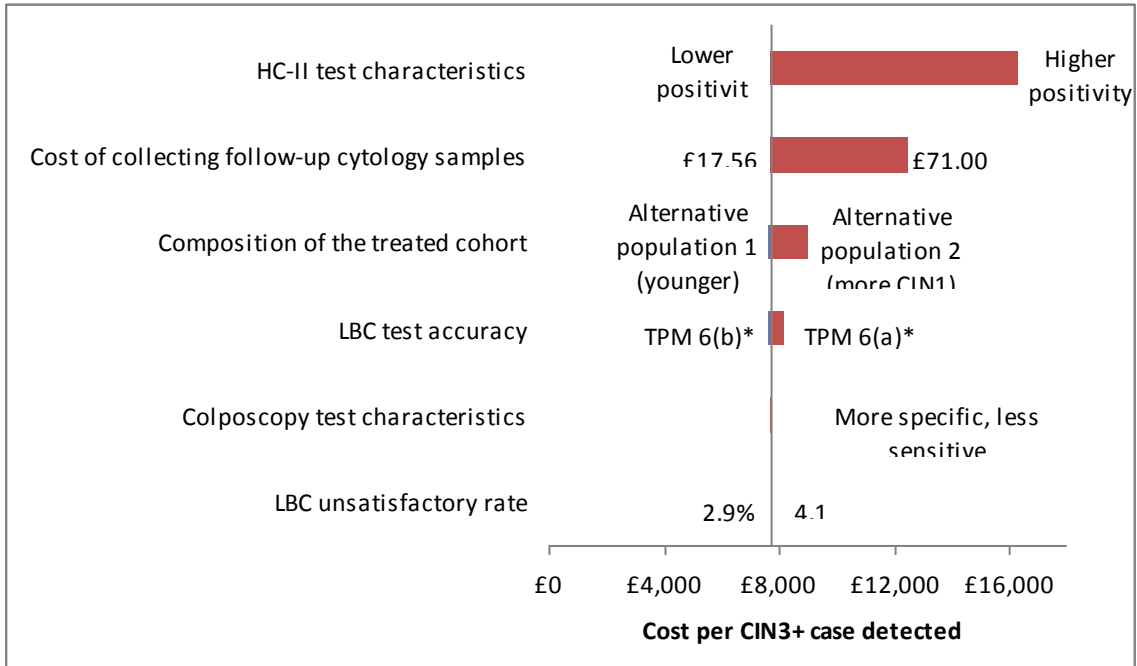
b) HPV testing – HPV Sentinel sites study protocol



Alternative populations are described in an Appendix.

* TPM 6(a) and TPM 6(b) refer to a set of test characteristics for LBC. They are described more fully in an Appendix

c) HPV testing – Kitchener protocol

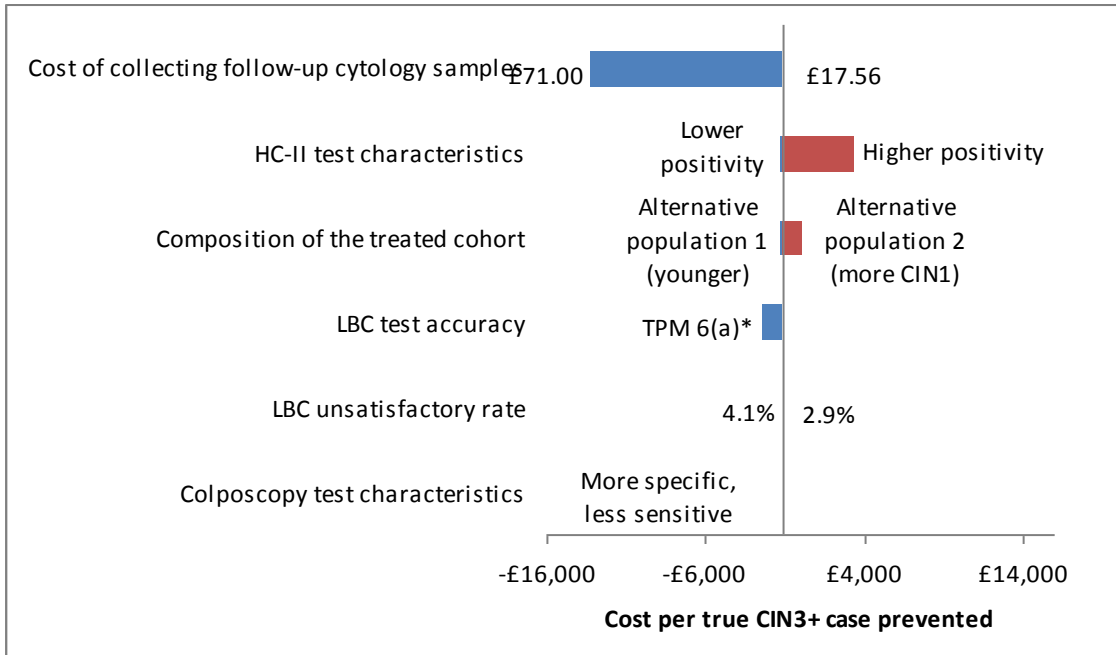


Alternative populations are described in an Appendix.

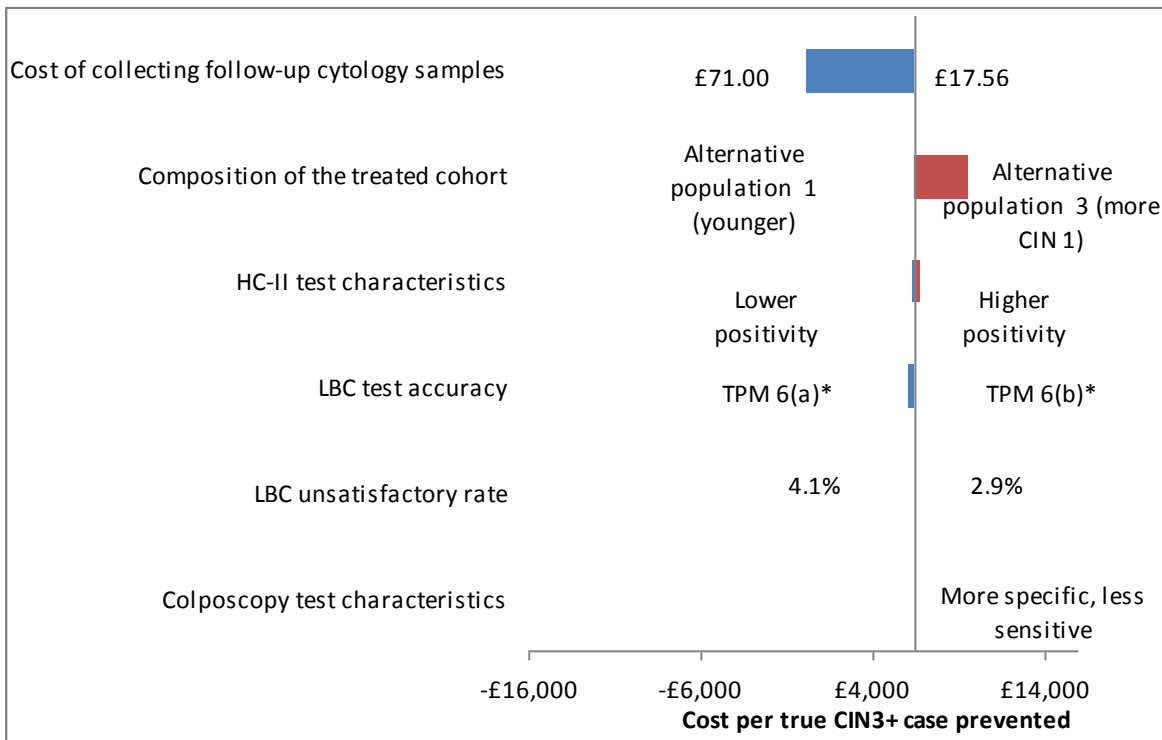
* TPM 6(a) and TPM 6(b) refer to a set of test characteristics for LBC. They are described more fully in an Appendix.

Figure 6.4 Impact of various model assumptions on the cost per underlying CIN 3+ case averted at 10 years post-treatment, compared to current practice

a) HPV testing – HPV Sentinel sites study protocol



b) HPV testing – Kitchener protocol



Alternative populations are described in an Appendix.

* TPM 6(a) and TPM 6(b) refer to a set of test characteristics for LBC. They are described more fully in an Appendix.

7. DISCUSSION

In interpreting these results it must be kept in mind that due to the slightly late commencement of this study it was necessary to terminate data collection before all women had had time to complete all the stages of the protocol. Therefore the numbers of women are small in some of the later steps.

HPV testing as a triage for borderline and mild dyskaryosis

The HPV positive rate in the current study was greater than that observed in the earlier HPV/LBC pilot studies, despite the exclusion of women aged 20-24. The difference in HPV positive rates between the centres involved in this project highlights the inter-laboratory variation in grade classification, which may be reflected in any wider-roll out of HPV triage around the country in terms of rates of referral to colposcopy. Because only one site used both technologies we cannot determine whether the difference in positive rates between technologies is due to the technology or to other differences between the sites.

It is possible that the difference in HPV positive rates between sites is due to the threshold that different sites use to determine borderline and mild test results; those with a higher threshold tended to have a higher rate of HPV positivity. This is supported by the fact that the sites with high positivity rates have a very low 'mild to borderline' ratio. This suggests that sites with a low ratio may classify as borderline samples that would be classified as mild dyskaryosis in sites with a high ratio, and hence have a smaller number of mild tests (as they have been included in the borderline category). This would lead to a higher rate of HPV positivity, as these sites may also classify as mild dyskaryosis samples that would be classified as moderate elsewhere.

Furthermore the two sites with the lowest rate of HPV positive tests classify a higher percentage of all samples taken as borderline changes/mild dyskaryosis and a higher percentage of all tests as borderline dyskaryosis or worse than do the other sites, according a 3 year average from the NHSCSP screening returns. (KC61 part B:2006-07,2007-08, 2008-09)

As observed in other studies the rate of HPV positivity decreases with increasing age³⁶. Consequently women who are undergoing a test as a result of a first routine call, which should be at age 25, have a higher positive rate than women who are attending due to a routine recall. Age-adjusted HPV positive rates show that any differences between these two groups of women are due to age alone, and that reason for test does not impact on HPV positive rates.

The HPV positive rate is significantly higher in women with mild dyskaryosis compared to those with borderline cytology. Cytology grade also appears to be associated with the RLU value in HPV positive women; the median and mean RLU value is higher in every age group in women with mild dyskaryosis. This suggests that the RLU value may be linked to disease severity and offers a future possibility for refining HPV triage.

However there is no obvious relationship between RLU and disease severity or an abnormal outcome at colposcopy. The median RLU value actually decreases from CIN1 to CIN3, but does seem to be greater in women with CIN1 than in women who were negative at colposcopy. This may suggest that higher viral loads trigger the development of CIN, but are not necessary for it to progress to high grade CIN. Typing of HPV infection would be needed to explore these results further.

It might have been expected that the referral rate to colposcopy in this study would be lower than that observed in the earlier HPV/LBC pilot studies, as women who test negative for HPV at initial cytology were referred immediately to routine recall, as opposed to being retested and referred to colposcopy if they tested positive for HPV or had an abnormal cytology. In the event, due to the higher HPV positive rates observed the rate of referral to colposcopy in this current study (64%), is significantly higher than those observed in both the initial (62%) and the revised (42%) protocol of the earlier HPV/LBC pilot studies.

Among women with borderline cytology the rate was significantly higher than that observed either the initial (49%) or revised protocol (33%) of the earlier HPV/LBC pilot studies. Among women with initial mild dyskaryosis the referral rate was slightly higher in the initial pilot sites protocol (86%) than in the Sentinel sites study, but this difference was not significant. The Sentinel sites study referral rate was significantly higher than in the revised protocol (63%) in this group.

The overall rate of attendance for colposcopy for HPV positive women was 90.2%; there was no significant difference in attendance with cytological grade, although attendance did increase with increasing age. The age-specific rates are slightly lower than those observed in the earlier pilot study for HPV positive women referred directly to colposcopy, except in women aged 50-64 with initial mild dyskaryosis. However overall there was no significant difference in attendance rates between the two studies, which suggests that managing HPV positive women with direct referral is still acceptable in the larger population under investigation in this study.

The overall detection of high grade CIN in women attending colposcopy was 16.3%; the rate of CIN2 or worse decreased with age, but there was no evidence of a significant association with initial colposcopy result. This rate of detection is slightly lower than the 18.7% of colposcopies that were CIN2 or worse in HPV positive women referred directly to colposcopy in the earlier HPV/LBC pilot studies.

The positive predictive value (PPV) of a positive HPV test for detecting CIN2 or worse was greater in women with initial mild dyskaryosis than initial borderline cytology. When considering higher grades of CIN (CIN3 or worse) women with borderline cytology had a higher predictive value although this relationship was not significant. The PPV of HPV decreased with increasing age; a pattern which was also observed in the pilot sites study. However the PPVs were higher in the pilot sites study; 9.5% for CIN3 or worse and 20.1% for CIN2 or worse. This observed difference is likely to be due to the different sites participating in the two studies.

The age and BL: Mild Ratio standardised positive predictive values for CIN2 or worse range from 24.7% to 8.3% between sites, for CIN3 or worse they range from 12.3% to 2.5%. A higher HPV positive rate appears to be associated with a higher PPV for both CIN2 or worse and CIN3 or worse in all sites except Northwick Park. This may be due to the relatively high percentage of HPV positive women in Northwick Park who choose to go private and therefore whose results were unobtainable. It is possible that private health care was recommended if a high grade lesion was suspected.

There does not appear to be an association between PPV and percentage of women biopsied. The 3 sites with the lowest PPVs corresponded to the three sites with the highest rates of false positive referral in all women tested in a three year period. (KC61 part C1:2006-07, 2007-08, 2008-09)

Of those women who were negative for CIN at colposcopy 61.6% underwent a biopsy, and 56 women underwent an excision biopsy. This suggests that HPV triage could lead to a large proportion of women undergoing biopsy unnecessarily. However it is possible that in the absence of HPV triage the majority of these women would have eventually been referred to colposcopy following repeat cytology; current literature suggests the majority of them would have been³⁷. The type of biopsy chosen varied by centre, although all performed some excision biopsies, suggesting that 'see and treat' is still common practice.

For those women with CIN1 who were not treated, a follow up cytology was to be performed at 12 months. Attendance was low due to the time period between colposcopy and further management; however for those attending dyskaryosis persisted in almost 40%, which is substantially higher than that which would be expected at routine screening, and suggests that further follow up of this group is required.

HPV as a test of cure after treatment

Two groups of women were used to evaluate the use of HPV testing as a test of cure after treatment of CIN. In the first group, those who had progressed through the HPV triage route, the rate of treatment failure was 25.7%. Among women who had entered the study through the non-triage route the rate was significantly lower at 18.3% ($p=0.0003$). It is also of interest to note that in the triage group the main reason for failure was an abnormal cytology whereas in the non-triage group the opposite was true.

The positive predictive value of HPV in women with negative cytology for CIN2 or worse and for CIN3 or worse was significantly lower than that in women with an abnormal cytology. However the majority of women who failed test of cure due to an abnormal cytology were negative at colposcopy, so HPV testing may be more useful stratifying those women with an abnormal cytology after test of cure into high and low risk groups. In this study, women with abnormal cytology were not tested for HPV, so we cannot determine the PPV of positive HPV overall for test of cure.

However over 80% of women were negative for HPV allowing them to return directly to routine recall and bypassing the current post colposcopy management which may take up to ten years before a woman can be returned to routine recall. The sensitivity of HPV testing as a test of cure has been estimated to be up to 100%, however further follow up of these women would be required to ensure they remained disease free.

Turnaround of HPV testing

Some of the Sentinel sites were meeting the 14 day turn-around target between a cytology sample being taken and a woman receiving her result, as set by the government integrating HPV testing. This was achieved with a twice weekly HPV testing schedule as part of the 'Lean Implementation Project', however to ensure all sites meet this target daily HPV testing may be required.

Costs of HPV testing

We found that the main implementation component for the cytology laboratories was making changes to the Information Technology system, although no costs were substantive. Comparison of alternative delivery models indicated that by setting up HPV processing centres was set-up within existing cytology laboratory, in an 'integrated cytology/ HPV laboratory' generated savings in staff time ranging from between £2.54 to £4.86. The additional costs incurred by having a 'hub and spoke model' with cytology laboratories sending samples to another site for processing included the cost of transportation and extra administrative workload.

When considering alternative implementation options another important aspect is the additional cost of HPV testing which increase when running smaller batches if the Hybrid Capture II system is used. Overall our results indicate that with two testing centres per SHA it would be possible to have average batch sizes 60 samples per run, given a twice weekly testing schedule. Given that the cost per HPV test with this batch size is only an extra £1.20, this may also be a cost-effective option if transport costs are reduced, especially where the SHA covers a large geographic area. Whilst Hybrid Capture II was used within this evaluation, alternative options that require smaller batch sizes are also available.

An alternative approach would be to have one national laboratory or only a few very large laboratories. A further advantage of processing HPV tests at higher volumes is the potential to generate savings from economies of scale. For example, further HPV equipment could be used that increases the automation of the HPV testing process. The results of this project suggest that transport costs were significantly higher over longer distances, although it is possible that lower and more efficient transport options could be found such as transferring samples to a central point before sending on.

Women's preferences and utility

The published literature was reviewed to identify women's preferences for HPV testing. The majority of the studies indicate that women prefer HPV testing to repeat cytology tests. The studies indicate that although there may be a negative emotional effect associated with receiving a positive HPV test result, this is essentially short-term and is not apparent beyond six months. No statistically significant differences in utility scores were identified between alternative management strategies.

Cost-effectiveness of HPV triage

Modelling work from the original NHS LBC/HPV Pilot sites indicated that HPV triage for mild and borderline cytology tests is likely to be highly cost-effective in the UK setting⁸, and these findings are consistent with other published studies. This modelling work highlighted a large increase in referral rates to colposcopy. However, the impact on colposcopy workload will be highly dependent on local screening policy. There are policy variations nationally in the current management of mild and borderline cytology tests, both in the number of repeats prior to colposcopy and referral practice variations by age.

However, given the loss to follow-up with repeat cytology, risk of progression with delayed follow-up and women's preferences, HPV triage is likely to be a highly cost-effective option compared to repeat cytology.

Cost-effectiveness of 'HPV test of cure'

Modelling work within the HPV implementation project mainly focussed on using HPV testing as a 'test of cure', as there has been limited evaluation of this topic to date. Our results indicate that management of treated CIN based solely on the results of cytology and HPV testing at 6 months post-treatment (as implemented in the HPV Sentinel sites study) is associated with the lowest costs over 10 years compared with a strategy of annual follow-up with cytology (and colposcopy where indicated) and no HPV testing (current management guidelines). The modelling also indicated that HPV test of cure appeared to avert more cases of underlying CIN3+ at 10 years compared with current protocols. Therefore suggesting this is a highly cost-effective strategy.

A limitation of the 'HPV test of cure' modelling work is that predictions for detected CIN2/3+ recurrence over the first 10 years post-treatment are extrapolations based on data from studies with shorter follow-up periods, and are therefore not guarantees of safety. As cancer is a rarer outcome compared to CIN3, a reduction in CIN3+ does not necessarily imply a reduction in cancer cases.

Conclusions

Rates of referral to colposcopy increase with the introduction of HPV triage but the rates vary between sites, probably due to differences in classification of cytology. Triage would allow approximately a third of all borderline and mildly dyskaryotic women to be returned immediately to routine recall, thus reducing the burden on cytology services. The positive predictive value of a positive HPV test in those women for CIN2 or worse observed in this study was 16%, but again there will be variation between sites.

HPV testing on women with negative cytology as a test of cure had a low PPV for high grade CIN. However it allows the majority of women who are negative for HPV to be returned directly to routine recall, by passing the long management process normally associated with follow up after treatment.

To be cost-efficient, and to meet turn-around times, HPV testing needs to be conducted at HPV testing centres with sufficient throughput to run full batches of HPV tests. Running daily batches, this would only be possible with one HPV testing centre serving a group of cytology laboratories reading

over 300,000 slides annually... As savings can be generated by implementing HPV testing within a cytology laboratory compared with a 'hub and spoke' delivery model consideration should be given to this implementation option.

Taking into consideration the loss to follow-up with repeat cytology, risk of progression with delayed follow-up and women's preferences, HPV triage is likely to be a highly cost-effective option compared to repeat cytology.

Modelling of HPV test of cure would generate cost saving compared with current colposcopy management due to a reduction in colposcopy workload and is also slightly more effective at averting cases of CIN3+. Therefore, this is a highly cost-effective policy option.

Appendix 1

Step 1; Initial Borderline or mild Cytology							
ID number	Date of birth	Reason for smear	Cytology date	Cytology Result	HPV result	RLU	Management
	(mm/yyyy)	1=Routine call 2=Routine Recall 3=Previous abnormality 4=Previous inadequate smear 5=Opportunistic 6=Follow-up after treatment 7=Other		8=Borderline 3=Mild	P=positive N=Negative		RR=Routine 3 or 5 year recall Colp=Colposcopy (step2)

Step 2; Colposcopy						
ID number	Date of Referral Cytology	Colposcopy attendance	Colposcopy Date	Biopsy	Colposcopy Result	Management
	Must not be null	A=Attended P=DNA-went private M=DNA-moved NK=DNA-Reason not known	Must not be null (if attended)	1=No biopsy 2=Diagnostic (punch) 3=Excision 4=Other	cervical cancer AIS CIN3 CIN2 CIN1 HPV/cervicitis only Normal Inadequate Unknown	RC=No treatment cytology at 12 months (step 3a) T=Treatment then repeat cytology and HPV test (step 3b) RR=Routine 3 or 5 year recall (depending on age)

Step 3a; Repeat Cytology								
ID	Reason for cytology	Date of Referral colposcopy	Cytology attendance	Cytology Date	Cytology Result	HPV result	RLU	Management
	RC=Repeat cytology after untreated CIN1 (step 3a) T=Test of cure cytology/HPV after treated CIN (step 3b)	must not be null	A=Attended P=DNA-went private M=DNA-moved NK=DNA-Reason not known	must not be null (if attended)	1=Inadequate 2=normal 8=borderline 3=mild 7=moderate 4=severe 5=severe/invasive carcinoma? 6=Glandular Neoplasia	P=positive N=negative		RR= 3 year recall Colp=Colposcopy (step 4)

Step 3b; Treatment

ID number	Date of Referral Cytology	Colposcopy attendance	Colposcopy Date	Treatment	Colposcopy Result	Cytology Date	Cytology Result	HPV result	RLU	Management
	Must not be null	A=Attended P=DNA-went private M=DNA-moved NK=DNA-Reason not known	Must not be null (if attended)	1=No biopsy 2=Diagnostic(punch) 3=Excision 4=Other	cervical cancer AIS CIN3 CIN2 CIN1 HPV/cervicitis only Normal Inadequate Unknown	must not be null (if attended)	1=Inadequate 2=normal 8=borderline 3=mild 7=moderate 4=severe 5=severe/invasive carcinoma? 6=Glandular Neoplasia	P=positive N=negative		RR= 3 year recall Colp=Colposcopy (step 4)

Step 4; Repeat Colposcopy

ID number	Date of Referral Cytology	Colposcopy attendance	Colposcopy Date	Biopsy	Colposcopy Result	Management
	Must not be null	A=Attended P=DNA-went private M=DNA-moved NK=DNA-Reason not known	Must not be null (if attended)	1=No biopsy 2=Diagnostic(punch) 3=Excision 4=Other	cervical cancer AIS CIN3 CIN2 CIN1 HPV/cervicitis only Normal Inadequate Unknown	RC=Repeat Cytology T=Treatment then repeat cytology and HPV test RR=Repeat smear in 3 or 5 years

Test of cure: High Grade or persistent low grade cytology with treated CIN

History								Test of Cure					
ID	Date of Birth	Cytology History	Date of referral cytology	Biopsy histology	Date of biopsy	Treatment Histology	Date of treatment	Cytology attendance	Cytology Date	Cytology Result	HPV result (if cytology is normal)	RLU	Management
		1=High grade cytology 2=Persistent low grade cytology		CIN3 CIN2 CIN1	must not be null	CIN3 CIN2 CIN1	if different to date of biopsy	A=Attended P=DNA-went private M=DNA-moved NK=DNA-Reason not known	must not be null (if attended)	1=Inadequate 2=normal 8=borderline 3=mild 7=moderate 4=severe 5=severe/invasive carcinoma? 6=Glandular Neoplasia	P=positive N=negative		RR= 3 year recall Colp=Colposcopy (step 4)

Appendix 2: Sentinel sites study LBC laboratory costing questionnaire

SECTION 1: HPV RELATED STAFF COSTS

Q1. Please specify who is responsible for each of the activities (current staff only) and whether they required any training

List of activities	Please give their staff grade	Please briefly describe any training provided – if required	If so, how much staff time was required for training?	How much did the training cost? (if relevant)
Identifying samples for HPV testing				
Packaging samples				
Updating clinical records with HPV results				

If you have any comments on training, please describe below:

SECTION 2: TRANSPORT COSTS

Q2. How many times a week are LBC samples sent to HPV test centres for HPV testing?	
Q3. What is the cost per journey of transporting samples to HPV test centres?	
Q4. On average how many samples are sent each journey	
Q5. What is the maximum number of samples that can be sent at a time for the same price?	

If you have any comments on transport cost, please describe below:

SECTION 3: OTHER COSTS

Q6. Did you have to change the IT system because of HPV testing? **Yes**
No
(please tick as appropriate)
If no, please ignore **Q7 & Q8**.

Q7. If yes, how much staff time was spent on IT system changes?
If you have any comments on this, please describe below:

Q8. If yes, how much money was spent on IT system changes?
If you have any comments on this, please describe below:

Q9. Was any smear taking training on HPV required? **Yes**
(please tick as appropriate)
No
If no, please ignore **Q10 to Q12**

Q10. If yes, how many smear takers were trained?

Please briefly describe what the training involved:

Q11. If yes, how much staff time was spent providing smear taking training?
If you have any comments on this, please describe below:

Q12. If yes, how much money was spent on smear taker training?

If you have any comments on this, please describe below:

Q13. If there were any further costs associated with HPV testing for your cytology laboratory please describe below. (Please note that we will cost colposcopy and biopsy separately based on the observed workload)

Thank you for your time in completing this questionnaire.

Appendix 3: Sentinel sites study HPV laboratory costing questionnaire

SECTION 1: STAFF COST

Q1. Please specify following information about the current staff.

Staff grade	Identify the role of current staff for the performing the HPV testing	Details of any training received by current staff for HC-2	Details of time required for the training mentioned	Cost of training	Describe how training was delivered

If you have any comments on training, please describe below:

SECTION 2: HPV HC2 (QIAGEN) EQUIPMENT COST

Q2. For HPV DNA testing which type of HC2 equipment have you been using? (please tick as appropriate)

- Manual
- Automatic

Q3. How much was spent on 'HC2 equipment'? (please tick the relevant one and provide price)

- Leased price _____ Length of lease _____
- Purchased price _____

Q4. How much was each 'HC2 kit'?

SECTION 4: NON-QIAGEN CONSUMABLE COST

Q6. Please specify information on the cost of non-digene consumables

List of Non-Qiagen consumables	Unit Volume (litre, box)	Unit cost per box or per litre	Quantity required per test

If there are other costs and/or if you have any comments on this section, please describe

Thank you for your time in completing this questionnaire.

Appendix Table 4: Training to identify samples for HPV testing in cytology laboratories

	Activity/site	A	B	C	D
Training to identify samples for HPV testing	Grade and type of staff trained	BMS2 b and 7	Trainee cytoscreeners	BMS 3/4	BMS 2 BMS 1 Cytoscreeners
	Training provided	Training on access database	How to find pots, where to place number up	NA	Lectures and protocols
	Staff time required for training	2 hours	10 minutes per person.	NA	1 hour
Training in packing samples	Staff grade	Band 3 MLA	BMS	BMS 2	BMS 1 BMS 2
	Training provided	Explained list presented To ensure correct total	Health & safety guidance How to pack, book courier etc	NA	Protocols and verbal explanation
	Staff time required for training	2 hours	15 mins per person	NA	½ hour
Updating clinical records with HPV results	Staff grade	BMS2 Band 7	Chief BMS	BMS 2	BMS 2
	Training provided	Retrieve & save result from NHS Net Enter the correct report code QC to reduce transposition errors and hard copy reports	How to fill in spreadsheets, updating records, progression steps	Use of database	Protocols and verbal explanation
	Staff time required for training	2-3 hours	20 mins	½ day	½ hour

* Advanced Biomedical Scientist Practitioners

Appendix Table 5: Smear takers training cost

Site	A	B	C	D
Was any smear taking training on HPV required?	Yes	Yes	yes	Yes
How many smear takers were trained?	212	76	52	200
Please briefly describe what the training involved:	Training included what is HPV, HPV Transmission, HPV Triage protocol, HPV Test, Call and recall of patients receiving HPV triage, HPV Test of cure protocol	76 trained cascaded to colleagues	Held Q&A session for practice nurses & GP after HPV information packs had been distributed	Two formal presentations of 3 hours each plus a member of staff went to visit each GP practice where there had been no representation at either event
If yes, how much staff time was spent providing smear taking training?	6 hours 6 primary care sessions, each lasted for approximately one hour	15 hours 3 events for GP's/PN's, training for clinics at 2 main sites	2 days (approx)	12 hours - Six hours formal presentation plus individual visits
If yes, how much money was spent on smear taker training?	None The sessions were supported by the regional QA office	£1941 Sponsorship of £500 gained so cost was £1441 in real terms	£100 Room were not charged for a number of training sessions	£2500 Training was funded by the NHSCSP, PCT and drug companies

Appendix Table 6: Training to staff in HPV laboratory

Site 1

Staff grade	Identify the role of current staff for the Sentinel sites study performing the HPV testing	Training received by current staff for HC-2	Time required for the training mentioned	Cost of training	Describe how training was delivered
MLA	<ul style="list-style-type: none"> ● Labelling of samples ● Sample processing 	In-house	1 week	N/A	Hands on in the lab
BMS	<ul style="list-style-type: none"> ● Sample entry onto laboratory system ● HC2 Assay ● Reporting 	In-house	1 week	N/A	Hands on in the lab
Clerical staff	<ul style="list-style-type: none"> ● Booking in patient demographics ● Scanning request cards ● Printing and posting results 	Routine procedures			

Site 2

Agenda for change staff grade	Identify the role of current staff for the Sentinel sites study performing the HPV testing	Training received by current staff for HC-2	Time required for the training mentioned	Cost of training	Describe how training was delivered
8	Trouble shooting occasional running of assay	Digene training	3 days	None	On site technician 2 days, then validation of first run
7	Running assay	Digene training	Same as above	Same as above	Same as above
5	Running assay	Digene training	Same as above	Same as above	Same as above
4	Receipting and preparing samples	In house training	0.5 days	Staff time	In house observing and being supervised
2	Receipting and preparing samples	In house training	0.5 days	Staff time	In house observing and being supervised

Appendix Table 7: Cost of IT system change

Site	A	B	C	D
Did you have to change the IT system because of HPV testing?	yes	yes	yes	yes
If yes, how much staff time was spent on IT system changes?	2-3 days	4 days	4 days	2 days
If yes, how much money was spent on IT system changes?	none	£2250	none	None

Appendix Table 8: Transport cost

Site	A	B	C	D
How many times a week are LBC samples sent to HPV test centre?	2	2	2	2
Cost per journey	£5 for 10-16 samples £25 for 40+ samples	£40 + packaging	£50	£5 for 12 samples in a box
On average how many samples are sent each journey	10	18	15	13
Distance from HPV testing laboratory in KM	49	293	158	47
What is the maximum number of samples that can be sent at a time for the same price?	Approx 200 for £25	NA	Up to 1 kg in weight	12 centrifuge tubes max per box
Average transport cost	£0.50	£2.20	£3.33	£0.38

Appendix Table 9: Utility and preference study review

Study	Method	Respondents	Type/ question addressed	Finding
Philips <i>et al</i> (2006) ²⁷ England	WTP study Participants 1141	Women during routine consultation	Predict the impact of adding HPV triage on screening participation	(81.5%) of respondents willing to pay for a pap smear – of these (72%) would be willing to pay extra for HPV triage Adding HPV triage to cytology program increased average valuation by 47%. Valuation unchanged with about sexual transmission..
Howard <i>et al</i> (2008) ³¹ Australia	Health utility - SG Patients asked to trade between scenarios using a two stage SG method Participants 67	Women who were eligible for screening	Experiment to test process utility between pap smear and HPV test	HPV testing had lower process utility than cytology tests
McCaffery <i>et al</i> (2008) ³⁴ Australia	General preference study as part of randomised trial Participants 106	Women aged 16-70 years were recruited from 18 family planning clinics across Australia	Assess preferences for HPV triage	65% choose to have HPV test. Women who had children, had a previous abnormal Pap smear and who were more anxious about their abnormal result were More likely to choose HPV testing
Melnikow <i>et al</i> (2002) ³⁰ USA	Health utility - SG Structured interview of 170 women	Participants recruited from 5 family planning clinics in Northern California's Central Valley	Evaluate women's preference for early colposcopy versus repeat cytology tests	Mean difference in utilities for repeat pap smear and early colposcopy were small. Wide variation in women preference is observed, where unmeasured factors contributed substantially to variation.
Maissi <i>et al</i> (2005) ²⁹	Health utility- EQ-5D Postal survey	Women recruited from two centres participating in a NHS pilot study of HPV/LBC testing	Utility with/out HPV testing was assessed	Abnormal smear and HPV + result raised anxiety. Highest anxiety when abnormal pap, but HPV untested. Anxiety didn't exist in 6 months follow up

UK	Participants 1376			
Whynes <i>et al</i> (2008) ²⁸ UK	WTP study & EQ-5D Trial exit survey Participants 190	Women participated in TOMBOLA RCT	Compared WTP between repeated cytology and immediate colposcopy	No significant differences found between arms. VAS scores indicate higher QoL HPV triage group first at 12 months – no difference afterwards
Birch <i>et al</i> (2003) ³² UK	Health utility - SG Participants 170	Women attending family planning clinics in California that had a pap smear before	Evaluated process utility associated with repeated cytology and immediate colposcopy	Relative preference for HPV testing over repeat cytology depends on underlying pathology
Ferris <i>et al</i> (1997) ³³ USA	General preference study Participants 968	A convenience sample of 968 women	Evaluated women's preference for ASCUS and LSIL pap smear results	Most women preferred repeat pap smear if the index report was ASCUS and colposcopy if the initial report was LSIL.

Appendix 10

Data sources and model assumptions for post treatment management of CIN

Appendix Table 10.1 Definition of model health states.

Model health state	Gold standard definition
Normal	HPV PCR negative; negative histology
HPV	HPV PCR positive; negative histology
CIN 1	CIN 1 histology
CIN 2	CIN 2 histology
CIN 3+	CIN 3 histology or cervical cancer

CIN = cervical intraepithelial lesion; PCR = polymerase chain reaction

Model cohort - women treated for CIN

We assumed an initial age & disease distribution among treated women consistent with that seen at the HPV Sentinel sites study (personal communication, Rachel Kelly, Institute of Cancer Research, London) (see Appendix 10.2). Women included in the protocols meet eligibility for the National cervical cancer screening programme and are in the age range of 25-64 years, therefore our analyses assumes that women outside this age range are not in the population treated for CIN. Some of the HPV Sentinel sites study used HPV triage in the management pathway leading to initial treatment, and so the population seen at colposcopy and subsequently treated may differ (in terms of age and grade of disease) from that seen under current NHS guidelines.

For sensitivity analysis, we constructed alternative, theoretical treatment populations, with differing age and/or incoming CIN grade distribution at the time of treatment. The source of data for each population is summarised in Appendix Table 10.2. Populations 1 -3 will be based on a cohort of women treated for CIN in London, Manchester, and Aberdeen, described in Kitchener et al (2008)¹⁸. Population 1 has an age distribution consistent with the Kitchener study cohort (in which 73% of the treated population were aged less than 35 years), while the CIN distribution remains consistent with that seen at the HPV Sentinel sites. Population 2 has a distribution of CIN1 vs CIN2+ consistent with the Kitchener study cohort (in which 24% were treated for CIN1, and 76% for CIN2+), and an age distribution consistent with the HPV Sentinel sites. Population 3 is consistent with the Kitchener study cohort both in terms of age and grade of CIN distribution at baseline.

Appendix Table 10.2 – Data sources and assumptions used for age and disease characteristics of theoretical model populations of treated women

Population	Age distribution of population	Disease distribution at the time of treatment	Includes women outside screening age range?
Primary analysis population	HPV Sentinel sites	HPV Sentinel sites	No
<i>Alternative population 1</i>	<i>Kitchener (BJOG 2008)¹⁴</i>	<i>HPV Sentinel sites</i>	<i>No</i>
<i>Alternative population 2</i>	<i>HPV Sentinel sites</i>	<i>Kitchener (BJOG 2008)¹⁴</i>	<i>No</i>
<i>Alternative population 3</i>	<i>Kitchener (BJOG 2008)¹⁴</i>	<i>Kitchener (BJOG 2008)¹⁴</i>	<i>No</i>

Populations in italics are used for sensitivity analysis

The various parameter value combinations are shown in Appendix Table 10.3 below (values in bold are used in the primary analysis; values in square brackets refer to alternative populations 1-4 as described above).

Appendix Table 10.3 - Characteristics of the treated cohort – age and CIN grade distribution at the time of initial treatment

Age (years)	Proportion by CIN grade within each age group (%) [value sets used in sensitivity analysis]			Proportion of total CIN treatment population who are within each age group (%) [value sets used in sensitivity analysis]
	CIN1	CIN2	CIN3+	
30 (25 – 34)	7 [8, 20, 21]	33 [32,37,37]	60 [60, 43, 42]	63 [73, 63, 73]
42 (35 – 49)	13 [12*, 29*, 30]	31 [31,35,34]	56 [57, 36, 36]	35 [25,35, 25]
57 (50 – 64)	40 [41, 41, 40]	21 [21,29,30]	39 [38, 30, 30]	2 [2, 2, 2]
% of total treated	10 [9.7, 23.6, 23.6]	32 [31.8, 36.1, 36.1]	58 [58.6, 40.3, 40.3]	100

Baseline values used for the primary analysis are shown in **bold**. Some values were derived from or chosen in order to satisfy the targets for other parameters

Treatment success

We assumed that either loop electrosurgical excision procedure (LEEP) or cone biopsy are used for treatment of CIN. Both treatments are assumed to have the same properties in terms of treatment success.

We assumed that women treated for CIN can either be successfully treated (return to model health states of Well or HPV), treatment can be unsuccessful (remain in their initial CIN state), or can be partially successful (women treated for CIN2/3 can return to a health state of CIN1, as their original lesion represented a mix of CIN grades, and only the higher grade CIN has been removed by treatment). The proportion in each of these groups was set such that histological detection of CIN at the 6 month visit was consistent with that found in Kitchener et al ¹⁸. We assumed that no less than 95% would be successfully treated, based on NHS guidelines which stipulate that the proportion of confirmed treatment failures should not exceed 5% within 12 months of treatment ¹⁹. We assumed that 15.8% of women who are successfully treated remain HPV positive, consistent with the findings of a systematic review ¹¹. The final proportions used are shown in Appendix Table 10.4.

Appendix Table 10.4 Treatment success for CIN

Originally treated for	Model health state at 6 month visit (%)			
	Well or HPV *	CIN 1	CIN 2	CIN 3
CIN 1	96.3	3.7	-	-
CIN 2	96.3	2.5	1.2	-
CIN 3	96.3	2.5	-	1.2

* Of these women, 84.2% are in the Well health state (negative for HPV), and 15.8% are in the HPV health state

Recurrent disease post treatment

Those treated for CIN1 are assumed to be histologically negative for CIN following successful treatment, but may still be HPV infected. They follow an HPV natural history consistent with the general at-risk population (i.e. if they HPV infected, the infection may persist, progress to CIN, or clear, at rates consistent with the general at-risk population; and if they are uninfected, they continue to have the same risk of a new HPV infection as other women their age). The HPV natural history model for the general at-risk population is based on previously published work.^{11;22;23}

In contrast, women treated for histologically confirmed CIN2+ follow a more aggressive HPV natural history in light of their increased risk for CIN2+. We assumed that among women developing recurrent disease, 32.1% develop CIN2, and 67.9% develop CIN3+³⁸⁻⁴⁰. The evidence was reviewed to identify the risk of recurrent disease post treatment. We also assume that a small proportion of both HPV-positive and HPV-negative patients would have recurrent disease 1 year after successful treatment. Model predictions of CIN2/3 recurrence were calibrated to published data, as described on page 87. A review of the literature was performed^{11;18;26;35;38-43}. Based on this, we derived the relative risk of developing recurrent disease after the successful treatment according to post-treatment HPV status.

Cost data

See table 6.2 of the report

Assumptions

- i) HPV testing is performed at follow-up visits only when cytology is negative
- ii) Post-treatment visits which do not explicitly involve colposcopy (e.g. visits for cytology sampling) are assumed to be performed in the community and not in the hospital clinic (low cost scenario). During sensitivity analysis, we will also examine a higher cost scenario, where some women have these follow-up visits at a hospital clinic.

Compliance with management recommendations

In the base case analysis, compliance rates are based on 2007-2008 statistics from the Cervical Screening Programme in England²⁴ and a UK study using similar management in a group of women treated for CIN¹⁸. We also considered a scenario where there was perfect compliance with all management recommendations (best case scenario). Women who do not attend a follow-up visit are assumed to have the same probability of attending for a new smear as the general population, unless they re-attend earlier as a result of cancer symptoms. Subsequent management of women who return

for routine screening after missing an appointment is as for other women previously treated for CIN who have returned to routine screening.

Appendix Table 10.5 - Compliance with management recommendations

Parameter	Base case value	Range for sensitivity analysis
Compliance with colposcopy recommendation †	84 % ²⁴	84 % – 100 % *
Compliance at 6 month follow-up visit	100 %	-
Compliance at 12 month visit (among those who attended at 6 months):	85 % ¹⁸	85 % - 100 % *
Compliance at 24 month visit (among those who attended at 12 months)	83 % ¹⁸	83 % - 100 % *
Compliance with (re-)treatment	100%	-

† Based on did not attend (DNA) rates for follow-up colposcopies * Assumption

Screening compliance

We used registry data from Oxfordshire to estimate the cumulative re-screened proportion at various times after a negative smear for women who appeared on the register ⁴⁴. From this, and age-specific coverage data²⁴, we derived an interval specific probability of a woman attending for routine screening. This allowed us to include the impact of some early and late re-screening. As the data was derived from a region and at a time where three-yearly screening was recommended for all ages, we only applied these to women with a recommended screening interval of 3 years (ages 25-49). For women with a recommended screening interval of 5 years (ages 50-64), we assumed there would be no early or late re-screening, but that all women would re-attend every 5 years.

LBC parameters

Inadequate sample rates for LBC are based on 2007-2008 statistics from the Cervical Screening Programme in England ²⁴. A range was considered in sensitivity analysis based on the rates found in GP and NHS hospital settings.

Appendix Table 10.6 - Modelled test characteristics—LBC

Parameter	Base case value	Range for sensitivity analysis
Inadequate rate	3%	2.9% - 4.1%

Estimates of the test accuracy of LBC was based on previous work ^{22,23}. In the model LBC is characterised by a test probability matrix (TPM). For a given model health state (i.e. true underlying state), this gives the probability associated with each possible cytology result category. During sensitivity analysis we examined alternative sets of assumptions. They varied from the baseline assumptions as shown in Appendix Table 10.7.

Appendix Table 10.7 Summary of accuracy of alternative LBC test characteristics examined in sensitivity analysis, relative to baseline LBC test characteristics

TPM	Compared to baseline assumption:			
	Sensitivity for CIN2+ * [relative to baseline]	Specificity for no CIN, no HPV†	Positivity for HPV infections (no CIN)†	Sensitivity for CIN1†
5b	Lower [- 1%]	Lower (1)	Higher (1)	Lower (1)
6a	Highest [+6%] (2)	Lowest (3)	Higher (2)	Lowest (3)
6b	Higher [+5%] (1)	Lower (2)	Highest (3)	Lower (2)

When more than one set is higher or lower than baseline, ascending numerical rankings indicate increasing differences from baseline i.e. (1) is closer to baseline than (2) * at test threshold of borderline † Not independent variables; parameter follows from assumptions about CIN 2+ sensitivity

Colposcopy parameters

Sensitivity

The model uses a test probability matrix for colposcopy to specify the relationship between each possible underlying natural history health state at the time of testing and the colposcopy result. In the model, this information was used to specify the probability that a biopsy would be taken, according to the underlying health state (after unsatisfactory colposcopy results were excluded), as shown in Appendix Table 10.8 below. This data was based on a previous analysis^{22;23} and data from the HPV Sentinel sites study (personal communication, Rachel Kelly, Institute of Cancer Research, London).

Appendix Table 10.8 - Modelled test characteristics—colposcopy

Model health state	Probability that a biopsy will be taken at colposcopy (%)
Normal	73.8
HPV	73.8
CIN 1	79.2
CIN 2	90.8
CIN 3+	90.8
Cancer	100.0

Unsatisfactory rate

The same data were also used to derive an age-specific probability of unsatisfactory colposcopy (Appendix Table 10.9), which was used in the model.

Appendix Table 10.9 - Probability that colposcopy will be unsatisfactory—modelled values.

Age (years)	Probability that colposcopy will be unsatisfactory (%)
15–24	2.01
25–29	2.78
30–34	6.03
35–39	7.50
40–44	12.56
45–49	19.58
50–54	30.98
55–84	45.66

In the model, the probability that a follow-up colposcopy would also be unsatisfactory (that is, when performed after an initial unsatisfactory colposcopy) was specified as 91.74 per cent.

Hybrid Capture II parameters

Hybrid Capture II (HC-II) positivity rates for histologically confirmed CIN 2 and CIN 3+ were derived from a summary of meta-analyses of HPV testing.⁴⁵ Methods used to estimate test positivity in women in other health states has been described previously²².

Appendix Table 10.10 Assumed test characteristics of Hybrid Capture II (HC-II) HPV test, based on international data *

Model health state	Gold standard used	Hybrid Capture II positivity rate	
		Baseline (%)	Range (%)
Well	Cytology & PCR	1.4	1.4 – 4.2
HPV	PCR	49.7	49.7 – 92.5
CIN 1	Histology	84.2	69.4 – 98.9
CIN 2	Histology	94.4	90.9 - 97.9
CIN 3+	Histology	94.4	90.9 - 97.9

Abbreviations CIN = cervical intraepithelial neoplasia * Ranges given are derived from the literature and used in sensitivity analysis.

Model validation

CIN detected at 6 month visit

Histological CIN status at 6 months post treatment was available from the HPV Sentinel sites study, and for a cohort of women treated for CIN in London, Manchester, and Aberdeen (described in Kitchener et al.)¹⁸. A summary of the range of CIN detection rates seen in both studies is shown in Appendix Table 10.11.

Appendix Table 10.11 - Histologically detected CIN at a follow-up visit 6 months after treatment

Group	CIN 1	CIN 2	CIN3
All treated women	1.4 – 2.7%	0.4 – 0.6%	0.5 – 0.6%
<i>Model prediction</i>	2.5%	1.2%	

Source: Kitchener¹⁸ and data from HPV Sentinel sites study (personal communication Rachel Kelly, Institute of Cancer Research, London UK).

* Either cytology borderline or worse, or Hybrid Capture II positive

CIN detected at subsequent visits

Histological CIN status at 12 and 24 months post-treatment was available for a cohort of women treated for CIN in London, Manchester, and Aberdeen (described in Kitchener et al.)¹⁸. Model predictions were consistent with these findings (Appendix Table 10.12).

Appendix Table 10.12 - Histologically detected CIN 2+ at a follow-up visits 12 and 24 months after treatment

Cumulative % with CIN2+ by:	Kitchener 2008	Model prediction
12 months	1.7%	<i>1.3 – 1.7%*</i>
24 months	2.5%	<i>1.8 - 2.8%*</i>

* A range is presented based on varying compliance assumptions

Model predictions for histological CIN2/3 detected were also compared to findings in a cohort of women treated for CIN in British Columbia³⁵, and in a review article.⁴¹ As shown in Appendix Table 10.13, histological CIN rates at 6 years post-treatment were consistent with those found in British Columbia³⁵, for LEEP, assuming an age and index diagnosis distribution in the treated cohort consistent with the primary analysis population (described in Appendix Table 10.2).

Appendix Table 10.13 - Histologically detected CIN 2/3 in the first 6 years after treatment

Cumulative % with CIN2+ by 6 years:	Melnikow 2009³⁰	Model prediction
Assuming treatment with LEEP only	7.5% (95% CI: 6.6 – 8.3%)	<i>7.9%</i>
Average for treatment with cone, LEEP, and laser	7.8%	

Reference List

1. NHS. Office for National Statistics; Cancer Statistics Registrations. Series MBI No 37 2009;<http://www.statistics.gov.uk/statbase/Product.asp?vlnk=8843>.
2. Sasieni PD, Cuzick J, Lynch-Farmery E. Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer. The National Co-ordinating Network for Cervical Screening Working Group. *Br J Cancer* 1996;73:1001-5.
3. Peto J, Gilham C, Fletcher O, Matthews FE. The cervical cancer epidemic that screening has prevented in the UK. *Lancet* 2004;364:249-56.
4. Munoz N, Castellsague X, de Gonzalez AB, Gissmann L. Chapter 1: HPV in the etiology of human cancer. *Vaccine* 2006;24 Suppl 3:S3-1-S310.
5. Howell-Jones R, Bailey A, Beddows S, Sargent A, de SN, Wilson G, et al. Multi-site study of HPV type-specific prevalence in women with cervical cancer, intraepithelial neoplasia and normal cytology, in England. *Br J Cancer* 2010;103:209-16.
6. Castle PE, Lorincz AT, Mielzynska-Lohnas I, Scott DR, Glass AG, Sherman ME, et al. Results of human papillomavirus DNA testing with the hybrid capture 2 assay are reproducible. *J Clin Microbiol* 2002;40:1088-90.
7. Arbyn M, Paraskevaidis E, Martin-Hirsch P, Prendiville W, Dillner J. Clinical utility of HPV-DNA detection: Triage of minor cervical lesions, follow-up of women treated for high-grade CIN: An update of pooled evidence. *Gynecologic Oncology* 2005;99.

8. Legood R, Gray A, Wolstenholme J, Moss S. Lifetime effects, costs, and cost effectiveness of testing for human papillomavirus to manage low grade cytological abnormalities: results of the NHS pilot studies. *BMJ* 2006;332:79-85.
9. Moss S, Gray A, Legood R, Vessey M, Patnick J, Kitchener H. Effect of testing for human papillomavirus as a triage during screening for cervical cancer: observational before and after study. *BMJ* 2006;332:83-5.
10. Cuschieri KS, Cubie HA. The role of human papillomavirus testing in cervical screening. *J Clin Virol* 2005;32 Suppl 1:S34-S42.
11. Paraskevaidis E, Arbyn M, Sotiriadis A, Diakomanolis E, Martin-Hirsch P, Koliopoulos G, et al. The role of HPV DNA testing in the follow-up period after treatment for CIN: a systematic review of the literature. *Cancer Treat Rev* 2004;30:205-11.
12. Curtis L. Unit Costs of Health and Social 2008. Kent : Personal Social Services Research Unit. University of Kent, Canterbury 2008.
13. Pay Circular (A for C) 1/2006. Pay conditions for NHS staff covered by the Agenda for Change (A for C) agreement. In. Employers N, editor 2006.
14. Kitchener HC, et al, ARTISTIC. A randomised trial of HPV testing in primary cervical screening. *Health Technology Assessment* 2009;13.
15. Sherlaw-Johnson C, Philips Z. An evaluation of liquid-based cytology and human papillomavirus testing within the UK cervical cancer screening programme. *Br J Cancer* 2004;91:84-91.

16. Moss S, Gray A, Marteau T, Legood R, Henstock E, Maissi E. Evaluation of HPV/LBC Cervical Screening Pilot Studies: summary of report to the Department of Health. Sheffield: NHSCSP 2004.
17. Martin-Hirsch P, Rash B, Martin A, Standaert B. Management of women with abnormal cervical cytology: treatment patterns and associated costs in England and Wales. *Br J Obstet Gynaecol* 2007;114:408-15.
18. Kitchener HC, Walker PG, Nelson L, Hadwin R, Patnick J, Anthony GB, et al. HPV testing as an adjunct to cytology in the follow up of women treated for cervical intraepithelial neoplasia. *BJOG* 2008;115:1001-7.
19. NHS Cancer Screening Programmes. Colposcopy and Programme Management: Guidelines for the NHS Cervical Screening Programme. NHSCSP Publication No. 20. 1-4-2004. Sheffield, UK, NHS Cancer Screening Programmes.

Ref Type: Generic

20. Eggington S, Hadwin R, Brennan A, Walker P. Modelling the impact of referral guideline changes for Mild Dyskariosis on colposcopy services in England. 24. 2006. NHSCSP.

Ref Type: Report

21. Canfell K, Barnabas R, Patnick J, Beral V. The predicted effect of changes in cervical screening practice in the UK: results from a modelling study. *Br J Cancer* 2004;91:530-6.
22. Medical Services Advisory Committee. Human Papillomavirus Triage Test For Women With Possible or Definite Low-Grade Squamous Intraepithelial Lesions. Vol.

Ref. 39. <http://trove.nla.gov.au/work/35947706?selectedversion=NBD44869226#> ed. 2009.

23. Medical Services Advisory Committee. Automation Assisted and Liquid Based Cytology for Cervical Cancer Screening.
<http://www.health.gov.au/internet/msac/publishing.nsf/Content/app1122-1> ed. 2009.
24. The Health and Social Care Information Centre. Cervical Screening Programme, England 2007-08 Data Tables. 28-10-2008.

Ref Type: Report

25. Strander B, Ryd W, Wallin KL, Warleby B, Zheng B, Milsom I, et al. Does HPV-status 6-12 months after treatment of high grade dysplasia in the uterine cervix predict long term recurrence? *European Journal of Cancer* 2007;43:1849-55.
26. Strander B, Andersson-Ellstrom A, Milsom I, Sparen P. Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population based cohort study. *BMJ* 2007;335:1077.
27. Phillips Z, Avis M, Whynes DK. Introducing HPV triage into the English cervical cancer screening program: consequences for participation. *Women Health* 2006;43:17-34.
28. Whynes DK, Woolley C, Philips Z. Management of low-grade cervical abnormalities detected at screening: which method do women prefer? *Cytopathology* 2008;19:355-62.
29. Maissi E, Marteau TM, Hankins M, Moss S, Legood R, Gray A. The psychological impact of human papillomavirus testing in women with borderline or mildly

- dyskaryotic cervical smear test results: 6-month follow-up. *Br J Cancer* 2005;92:990-4.
30. Melnikow J, Kuppermann M, Birch S, Chan B, Nuovo J. Management of the low-grade abnormal pap smear: what are women's preferences? *The Journal of Family Practice* 2002;51:849-55.
 31. Howard K, Salkeld G, McCaffery K, Irwig L. HPV triage testing or repeat PAP smear for the management of atypical squamous cells (ASCUS) on PAP smear: Is there evidence of process utility? *Health Econ* 2008;17:593-605.
 32. Birch S, Melnikow J, Kuppermann M. Conservative versus aggressive follow up of mildly abnormal pap smears: testing for process utility. *Health Econ* 2003;12:879-84.
 33. Ferris DG., Kriegel D., Cote L., Litaker M., Woodward L. Women's triage and management preference for cervical cytologic reports demonstrating atypical squamous cells of undetermined significance and low grade squamous intraepithelial lesions. *Archive of Family Medicine* 1997;6:348-53.
 34. McCaffery KJ, Irwig L, Chan SF, Macaskill P, Barratt A, Lewicka M, et al. HPV testing versus repeat Pap testing for the management of a minor abnormal Pap smear: evaluation of a decision aid to support informed choice. *Patient Education and Counselling* 2008;73:473-81.
 35. Melnikow J, McGahan C, Sawaya GF, Ehlen T, Coldman A. Cervical intraepithelial neoplasia outcomes after treatment: long-term follow-up from the British Columbia Cohort Study. *J Natl Cancer Inst* 2009;101:721-8.

36. Burk RD, Kelly P, Feldman J, Bromberg J, Vermund SH, DeHovitz JA, et al. Declining prevalence of cervicovaginal human papillomavirus infection with age is independent of other risk factors. *Sex Transm Dis* 1996;23:333-41.
37. Rebolj M, Bais AG, van BM, Boer R, Meering WJ, Helmerhorst TJ, et al. Human papillomavirus triage of women with persistent borderline or mildly dyskaryotic smears: Comparison of costs and side effects of three alternative strategies. *Int J Cancer* 2007;121:1529-35.
38. Cecchini S, Visioli CB, Zappa M, Ciatto S. Recurrence after treatment by loop electrosurgical excision procedure (LEEP) of high-grade cervical intraepithelial neoplasia. *Tumori* 2002;88:478-80.
39. Flannelly G, Langan H, Jandial L, Mana E, Campbell M, Kitchener H. A study of treatment failures following large loop excision of the transformation zone for the treatment of cervical intraepithelial neoplasia. *Bjog* 1997;104:718-22.
40. Rema P, Suchetha S, Thara S, et al. Effectiveness, acceptability and safety of LEEP Effectiveness, acceptability and safety of LEEP in Kerala, India: beginners' experience. Available from <http://www.iarc.fr>. 2007.

Ref Type: Generic

41. Soutter WP, Sasieni P, Panoskaltsis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. *International Journal of Cancer* 2006;118:2048-55.
42. Soutter WP, de Barros LA, Fletcher A, Monaghan JM, Duncan ID, Paraskevaidis E, et al. Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. *Lancet* 1997;349:978-80.

43. Chan BK, Melnikow J, Slee CA, Arellanes R, Sawaya GF. Posttreatment human papillomavirus testing for recurrent cervical intraepithelial neoplasia: a systematic review. *Am J Obstet Gynecol* 2009;200:422-9.
44. Canfell K, Sitas F, Beral V. Cervical cancer in Australia and the United Kingdom: comparison of screening policy and uptake, and cancer incidence and mortality. *Med J Aust* 2006;185:482-6.
45. Arbyn M, Sasieni P, Meijer CJ, Clavel C, Koliopoulos G, Dillner J. Chapter 9: Clinical applications of HPV testing: A summary of meta-analyses. *Vaccine* 2006;24 Suppl 3:S78-S89.