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# Evaluation of cervical screening strategies with adjunct high-risk human papillomavirus testing for women with borderline or mild dyskaryosis

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**The management of women with a smear read as borderline/mild dyskaryosis (BMD) found by cervical cancer screening is still under discussion as only few of these cases are associated with high-grade lesions. To determine the optimal screening strategy for these women, a simulation model of cervical cancer development was used that is based on high-risk human papillomavirus (hrHPV) infection. The current strategy of repeat cytological testing at 6 and 18 months after BMD was compared to strategies with adjunct hrHPV testing. Calculations were done for both conventional and liquid-based cytology as the primary screening tool. In comparison to current screening, adjunct hrHPV testing was more effective in preventing cancer and more woman-friendly (reduction in colposcopy referrals with outcome < cervical intraepithelial neoplasia (CIN2) of up to 56% and in repeat smears of 30–100%). In combination with conventional cytology, cost-effective strategies were the ones in which a sample for high-risk human papillomavirus (hrHPV) testing is collected at a return visit within 1 month or in which hrHPV testing is restricted to repeat smears taken at 6 and 18 months. For these strategies, co-collection of samples for hrHPV testing at baseline is not necessary which has organizational and cost advantages. In combination with liquid-based cytology, it was cost-effective to perform a reflex hrHPV test at baseline from the liquid-based specimen. Liquid-based screening was more effective than conventional screening, but annual diagnosis costs were €5 million higher (population size 16 million). In conclusion, our calculations indicate that implementation of hrHPV testing for the management of women with borderline or mild dyskaryosis (BMD) is feasible both in settings where conventional and liquid-based cytology is current practice.**


**Key words:** cervical cancer screening; human papillomavirus; borderline/mild dyskaryosis; models; cost-effectiveness

In the Netherlands, like many other western countries, cytological screening with Papanicolaou (Pap) smears has reduced the incidence of invasive cervical cancer.[1–3] However, Pap test characteristics remain less than optimal as there still are considerable false-negative rates.[4,5] Moreover, equivocal or mildly abnormal cervical smears read as borderline or mild dyskaryosis (BMD), which is equivalent to ASC-US/ASC-H/LSIL according to the Bethesda 2001 classification, occur rather frequently (in 2–5% of screened women[6–8]), but are associated with cervical intraepithelial neoplasia (CIN) grade 2 or worse in only 5–15% of the cases.[7,9–11]

Evolving understanding of the etiologic role of high-risk human papillomavirus (hrHPV) infection in cervical carcinogenesis[12,13] and advances in technologies for hrHPV detection have prompted exploration of hrHPV testing as an adjunct or primary screening tool.[14] As hrHPV infections occur frequently (35–50% in women with BMD smear[6,7]) and both the infection and the cervical abnormalities often regress,[15] evaluation of the (cost-)effectiveness of hrHPV testing in cervical screening is rather complicated and usually assessed with mathematical models.[16–20]

The current management of BMD smears in the Netherlands is to repeat cytology after 6 and 18 months and to refer for colposcopy if a second abnormal smear is found. There are several possibilities to optimize current screening. Firstly, the conventional Pap test may be replaced by a liquid-based Pap test that may have a higher sensitivity for detecting CIN lesions.[21,22] Secondly, the hrHPV test may be included as an adjunct screening tool as it has been shown that the sensitivity for CIN3 and invasive cancer increases when hrHPV testing is added to cytology.[5,23] Finally, a reduction in screening and diagnostic procedures may lower the burden imposed on the women participating in the screening.

In this study, we investigated the cost-effectiveness of hrHPV testing as an adjunct screening tool in women with a smear diagnosed as BMD, as compared to repeat cytological testing. We conducted a simulation study comparing the costs, burden, and effectiveness of repeat cytological testing and several screening strategies with adjunct hrHPV testing. Separate analyses were done for hrHPV testing strategies, with either conventional or liquid-based cytology as the primary screening tool. To generate simulations, we used a natural history model[24] based on recent data from studies on the prevalence and clearance of hrHPV infections and the incidence of cervical abnormalities in the Netherlands.[6,9,15,25,26]

## Material and methods

### *Mathematical model*

We used a Markov model that simulates the natural history of cervical cancer for a cohort of women, using Fortran90 software (Salford software, Manchester, UK). An extensive description of the model is available,[24] including detailed information about how the model parameters were estimated, a validation of the model predictions of the incidences of cervical cancer, CIN, and abnormal cytology against independent Dutch nationwide and population-based figures,[6,8,27] and a comparison with the number of high-grade lesions detected by cervical screening in a population-based UK study[7] and a population-based German study.[28] The model has 30 health states among which transitions are possible at 6-month intervals. The model predicts the health status of women from the age of 30 until age of 80. Cervical abnormalities developed at an earlier age are captured by specifying a starting distribution for the health states. The model variables are presented in Table I.

### *Etiologic assumptions*

The model assumes that hrHPV infection is a prerequisite for CIN3 and cervical cancer.[12,13] In the model, women are categorized as either healthy (Table I: state Well), carrying hrHPV (Table I: hrHPV infected), carrying hrHPV and having developed CIN (Table I: states hrHPV positive CIN1-3), or having developed

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**TABLE I –** MODEL ASSUMPTIONS: DISEASE PARAMETERS[1], SCREENING CHARACTERISTICS, AND COSTS[2]

| From | To | 6–month probability | References |
|---|---|---|---|
| Disease parameters[1] | | | |
| Well | HrHPV infected | .007–.017 | [6] |
| | HrHPV–negative CIN1 | .002 | [6] |
| | HrHPV–negative CIN2 | .0002 | [6] |
| HrHPV–negative CIN1/2 | Well | .51 | [25] |
| HrHPV infected | HrHPV–positive CIN1 | .10 | [26,29,30] |
| | HrHPV–positive CIN3 | .01 | [26,29,30] |
| | Well | .37 | [6] |
| HrHPV–positive CIN1 | HrHPV–positive CIN2 | .25 | [9,15,31] |
| | Pre–Well | .25 | [9,25] |
| HrHPV–positive CIN2 | HrHPV–positive CIN3 | .25 | [9,15,31] |
| | Pre–Well | .25 | [9,25] |
| HrHPV–positive CIN3 | Pre–Undetected FIGO stage 1 | .20 | [31–34] |
| | Pre–Well | .30 | [25] |
| Undetected FIGO stage 1 | Undetected FIGO stage ≥2 | .048 | [35] |
| | Detected FIGO stage 1 | .032 | [36,37] |
| Undetected FIGO stage ≥2 | Detected FIGO stage ≥2 | .30 | [36,37] |

| Test | Accuracy (%) | References | Procedure | Cost (€) |
|---|---|---|---|---|
| HrHPV testing by GP5+/6+ or HC2 | | [5,6,23,38] | Conventional cytological screening | |
| Analytic specificity | 100 | | First smear | 53 |
| Analytic sensitivity | 97 | | Repeat smear | 43 |
| Cytological testing | | | GP5+/6+ PCR-EIA testing | 26 |
| Specificity | | [6] | HC2 testing | 31 |
| Positive if ≥BMD | 98.5 | | Reflex hrHPV testing: co-collection | 1 |
| Positive if >BMD | 99.85 | | 2-visit hrHPV testing: second smear | 19 |
| Specificity 6-month repeat smear | | | Liquid-based cytological screening | |
| Positive if ≥BMD | 90 | | First smear | 60 |
| Positive if >BMD | 99 | | Repeat smear | 49 |
| Sensitivity conventional cytology | | [6] | GP5+/6+ PCR-EIA testing | 32 |
| Threshold CIN1, positive if ≥BMD | 50 | | HC2 testing | 33 |
| Threshold CIN1, positive if >BMD | 20 | | Diagnosis, treatment, follow-up | |
| Threshold CIN2, positive if ≥BMD | 65 | | CIN0 | 329 |
| Threshold CIN2, positive if >BMD | 40 | | CIN1 | 1410 |
| Threshold CIN3, positive if ≥BMD | 80 | | CIN2 | 1633 |
| Threshold CIN3, positive if >BMD | 50 | | CIN3 | 1776 |
| Sensitivity liquid-based cytology | | [21,22,39] | FIGO stage 1 | 8792 |
| Threshold CIN1, positive if ≥BMD | 70 | | FIGO stage ≥2 | 10359 |
| Threshold CIN1, positive if >BMD | 25 | | Palliative care | 5481 |
| Threshold CIN2, positive if ≥BMD | 80 | | | |
| Threshold CIN2, positive if >BMD | 50 | | | |
| Threshold CIN3, positive if ≥BMD | 85 | | | |
| Threshold CIN3, positive if >BMD | 55 | | | |
| Colposcopy + biopsy | | | | |
| Sensitivity | 100 | | | |
| Specificity | 100 | | | |

[1]The states benign hysterectomy, death by cervical cancer, and death by other causes are not shown. The states Pre–Well and Pre–Undetected FIGO stage 1 connect with Well and Undetected FIGO stage 1, respectively. The pre–states have been included to account for differences in regression and progression times. For instance, the time to progress from CIN3 to FIGO stage 1 was set at 10.6 years while the time to regress from CIN3 to Well was set at 1.5 years.–[2]Costs are in years 2004 Euros, and include patient time spending and traveling costs.

an invasive lesion (Table I: states undetected Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage1/≥2). A separate category consists of women who have developed CIN1 or CIN2 without an hrHPV infection (Table I: states hrHPV-negative CIN1/2). All states are pathological states that may differ from the states observed at screening.

For the regression and progression of preinvasive hrHPV-positive lesions, the following assumptions are used in the model. After infection with hrHPV, the progression to CIN3 may go directly or *via* a distinguishable period of intermediate neoplasia (CIN1/2).[40] Clearance of the hrHPV infection excludes further progression of cervical neoplasia and regression of cervical neoplasia cannot occur without viral clearance.[25] Viral clearance may precede regression of CIN in which case an hrHPV-negative lesion can be observed.[25] Invasive lesions can be detected by symptoms (Table I: states detected FIGO stage1/≥2) or by screening.

*Disease parameters*

For the estimation of the preinvasive part of the natural history model (CIN0 to CIN3), recent Dutch longitudinal data sets[6,15,25,26] were reanalyzed, in which conventional Pap smear results had been collected and in which hrHPV presence had been tested by GP5+/6+ PCR-EIA[41] or HC2 (Hybrid Capture 2, Digene, Gaithersburg, Md). The health starting distribution and the incidence of hrHPV infection were derived from the POBASCAM study, a population-based screening trial of 44,102 Dutch women,[6] the progression rate after hrHPV infection from long-term follow-up data of 2,250 women with normal cytology at intake[26] and the progression and regression rate of CIN from follow-up data of women with abnormal cytology at intake.[9,15,25] The progression rates for hrHPV-positive CIN0/1 were comparable with international figures.[29–31] The probabilities of the transition of CIN3 to FIGO stage 1 and the transition of FIGO stage 1 to FIGO stage 2 were based on published data collected outside the Netherlands[32–34] and Dutch data collected before the implementation of nationwide screening,[35] respectively. Cervical cancer symptom probabilities (Table I: from undetected FIGO 1/≥2 to detected FIGO 1/≥2) were based on reported UK screening and cancer incidence data.[36,37] For the survival probabilities and the incidence of hysterectomy, Dutch registry data were used.[1,35,42] Relative 5-year

survival probabilities in the model were 93% (FIGO stage 1, age < 45), 86% (FIGO stage 1, age ≥ 45), and 43% (FIGO stage ≥2).[1]

*Screening characteristics*

The sensitivity and specificity of conventional cervical cytology were estimated from the POBASCAM data.[6] Cervical smears are read according to the CISOE-A classification, and interpreted as normal (Pap1), borderline dyskaryosis (Pap2), mild dyskaryosis (Pap3a1), moderate dyskaryosis (Pap3a2), severe dyskaryosis (Pap3b), suspected of carcinoma *in situ* (Pap4), or suspected of carcinoma (Pap5).[8,43,44] A translation into the Bethesda 2001 classification is available.[8] The estimates are comparable to the ones reported in review studies.[4,23] For ThinPrep liquid-based cytology, sensitivity estimates were obtained from the literature.[21,39] The specificity of liquid-based cytology was set equal to the specificity of conventional cytology.[22]

The sensitivity of the hrHPV test fed to the model is the analytical sensitivity for detecting the virus.[38] The analytical sensitivity usually is higher than the clinical sensitivity for detecting CIN3 because hrHPV clearance may precede regression of the lesion.[25,38] In the model, the base-case analytical sensitivity of 0.97 (see Table I) corresponds to a clinical sensitivity for detecting CIN3 of 0.89, which is comparable to the clinical sensitivity of HPV DNA testing by GP5+/6+ PCR-EIA or HC2.[5,23]

*Cytological screening in the Netherlands*

Women between 30 and 60 years of age are invited to cytological screening at 5-year intervals. If the baseline smear is moderate dyskaryosis or worse (>BMD), the participant is referred to a gynecologist for colposcopy. If the baseline smear is borderline or mild dyskaryosis (BMD), the participant is recalled after 6 and 18 months and referred for colposcopy if a second abnormal smear is found (Fig. 1). If the gynecologist does not detect CIN, the participant returns to routine screening. Otherwise, treatment is applied and the participant is kept under surveillance of the gynaecologist, usually for a period of about 2 years.

*Alternative strategies for the follow-up of BMD smears*

The classical strategy of follow-up cytology after BMD was compared with strategies for the management of BMD with adjunct hrHPV testing (Fig. 1). The strategies were evaluated in combination with conventional and liquid-based cytology as the primary screening tool. In strategies A, B, and C, follow-up with combined hrHPV testing and cytology is applied after BMD. The recall dates are at 6 and 18 months (A), only at 6 months (B), or only at 12 months (C). In all these strategies, women who at the first recall present with an hrHPV-negative normal smear are referred back to the screening programme. In strategy A, women with >BMD and/or hrHPV presence at this recall are referred for colposcopy, whereas those with an hrHPV-negative BMD smear are recalled again at 18 months for both tests. In strategies B and C, all women with abnormal cytology and/or hrHPV presence at recall are directed to colposcopy. In strategies D, E, F, and G, BMD is followed by hrHPV testing at baseline. In combination with conventional cytology, baseline hrHPV testing can be performed either by co-collecting a sample for hrHPV testing (reflex testing, referred to as reflex) or by inviting women for a second visit within 1 month (2-visit testing, referred to as 2-visit). The sample required in case of reflex testing is collected irrespective of the cytological outcome and leads to an increase in the material and transportation costs. Follow-up hrHPV testing after 6 or 18 months is performed by co-collecting a sample for hrHPV testing. In combination with liquid-based cytology, baseline and follow-up hrHPV testing is performed on the liquid-based specimen. HrHPV-negative women are sent back to routine screening and hrHPV-positive women are directed to colposcopy in strategy D and recalled in strategies E, F, and G. The recall dates are at 6 and 18 months (E), only at 6 months (F), or only at 12 months (G).

*Costs*

Costs of screening include organizational costs,[45] traveling costs made by the participating women, and costs of production loss because of time spending[46] (Table I). True resource costs were used for the evaluation of conventional Pap, liquid-based Pap (ThinPrep2000 technology), GP5+/6+ PCR-EIA, and HC2 based on information from 2 laboratories (Department of Pathology, VU University Medical Centre, Amsterdam; Stichting Artsenlaboratorium en Trombosedienst, Utrecht). The costs of purchasing and transporting vials with liquid-based specimen were included in the liquid-based Pap cost price. These costs (estimated at €1 per smear, Table I) need to be added separately when reflex hrHPV testing is performed in combination with conventional cytology. Other separate costs are DNA extraction costs made when combining GP5+/6+ PCR-EIA with liquid-based cytology and sample conversion costs made when combining HC2 with liquid-based cytology. Note that when used in combination with conventional cytology, HC2 or GP5+/6+ PCR-EIA testing can be performed on the raw material, saving additional sample preparation costs.

For the treatment of preinvasive lesions, the medical, traveling, and time spending costs were summed.[46] The treatment percentages were set at 50, 80, and 100% for CIN1, CIN2, and CIN3, respectively. The percentages of lesions treated by hysterectomy were taken from the literature (5% for CIN1/2 and 11% for CIN3[47]). The non-hysterectomy treatments were divided in 95% LLETZ and 5% cone biopsy for CIN1, 90% LLETZ and 10% cone biopsy for CIN2, and 75% LLETZ and 25% cone biopsy for CIN3.[48] The costs of treatment and follow-up of invasive cancer and palliative care were taken from the literature[42,49] and converted to 2004 prices, using the consumer price index.[50]

*Analyses*

The effectiveness of screening was measured by the cervical cancer incidence reduction, gain in overall life expectancy, gain in cancer-free life expectancy, and the increase in negative predictive value of returning to routine screening (threshold CIN2). The cancer-free life expectancy was defined as the expected number of years before cancer had developed. For computing the negative predictive value, the histological status at the end of the 5-year screening interval was used. The screening burden for women was measured by the number of repeat smears and the colposcopy referral rate after a baseline BMD smear. The cost-effectiveness was assessed by comparing the discounted overall or cancer-free life expectancy per woman with the discounted lifetime costs per woman. The discounting rate was set at 3% per year. The presented figures are simulation averages. The cost-effectiveness analyses included computation of the efficiency frontier of nondominated strategies. A strategy is (extendedly) dominated if there exists a combination of other available strategies that is cheaper and more effective.[51]

By one-way sensitivity analyses, the robustness of the cervical cancer incidence and costs were examined with regard to changes in the performance of hrHPV testing (analytical sensitivity 93–99%; analytical specificity 97–100%), the performance of cytological testing (sensitivity of abnormal cytology lowered to 40, 55, and 70% for thresholds CIN1, CIN2, and CIN3, respectively; specificity of baseline cytology 96.5–98.5 %; specificity of 6-month repeat cytology 85–95%), the screening interval length (3–5 years), the disease parameters (base-case incidence hrHPV infection ±25%; base-case incidence CIN3 ±25%; base-case duration of CIN3 to FIGO stage 1 ±25%), the costs of treating a preinvasive lesion (base-case costs ±€500), and the costs of treating invasive cervical cancer (base-case costs ±€5000).

## Results

*Conventional cytology*

The results for strategies with conventional cytology and GP5+/6+ PCR-EIA for hrHPV testing are presented in Table II.

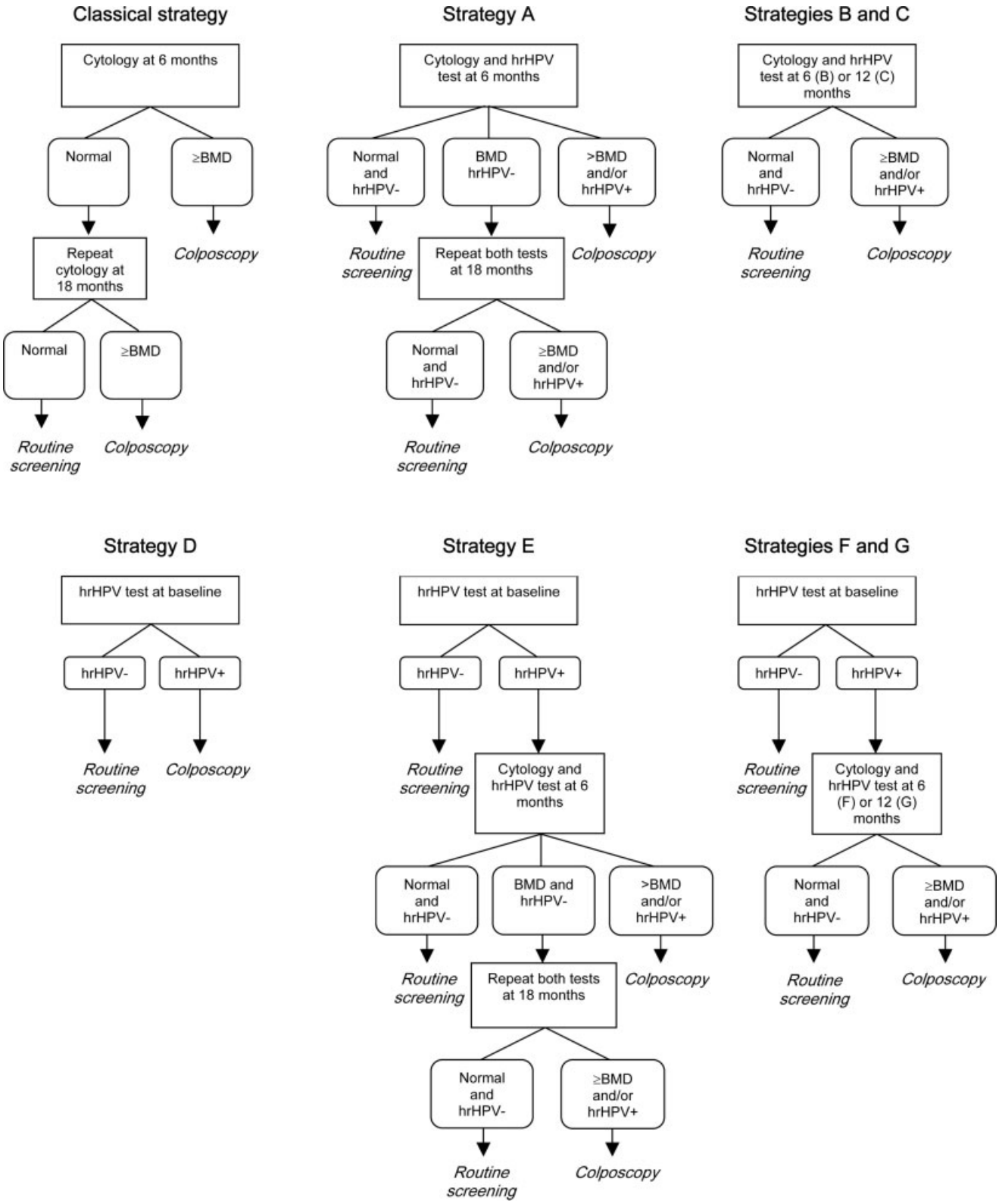


**FIGURE 1** – Classical and new strategies for management of BMD smears.

Compared to repeat cytological testing (classical strategy), adjunct hrHPV testing always resulted in an increase in negative predictive value. Except for scenario G, the addition of an hrHPV test also lowered the cervical cancer incidence. The largest incidence reduction (69.3% lower than in no screening situation) was obtained when all BMD smears were repeated once after 6 months (strategy B) or when women with an hrHPV-positive smear at baseline were immediately referred for colposcopy (strategy D).

**TABLE II –** SIMULATION RESULTS FOR CLASSICAL STRATEGY WITH FOLLOW–UP CYTOLOGICAL TESTING AFTER BMD AND SCREENING STRATEGIES WITH ADJUNCT hrHPV TESTING AFTER BMD (A–G)[1]

| Screening strategy | Reduction in cancer incidence[2] (%) | Screening summaries[3] | | | | | Discounted life expectancy and costs per woman from age 30 (discounting rate, 3% per year) | | | Annual nationwide diagnosis costs[4] (€) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | NPV (%) | Colposcopy referral rate | | Average number of follow–up smears | | Overall life expectancy (y) | Cancer–free life expectancy (y) | Lifetime costs (€) | |
| | | | No ≥CIN2 detected (%) | Total (%) | No ≥CIN2 detected | Total | | | | |
| No screening | | | | | | | 24.8753 | 24.6466 | 135.8 | |
| Conventional cytology | | | | | | | | | | |
| Classical | 68.4 | 98.4 | 13.7 | 27.7 | 1.5 | 1.8 | 24.9262 | 24.8515 | 286.1 | 35,150,000 |
| A | 69.2 | 99.4 | 10.9 | 25.1 | 0.9 | 1.1 | 24.9262 | 24.8537 | 285.0 | 35,083,000 |
| B | 69.3 | 99.4 | 19.1 | 33.8 | 0.7 | 1.0 | 24.9268 | 24.8545 | 288.4 | 35,254,000 |
| C | 68.7 | 99.4 | 10.3 | 23.9 | 0.8 | 1.0 | 24.9258 | 24.8516 | 282.8 | 34,953,000 |
| D (reflex) | 69.3 | 99.1 | 14.8 | 28.5 | 0 | 0 | 24.9263 | 24.8543 | 288.3 | 35,165,000 |
| D (2–visit) | 69.3 | 99.1 | 14.8 | 28.5 | 1 | 1 | 24.9263 | 24.8543 | 286.3 | 34,793,000 |
| E (reflex) | 68.8 | 99.0 | 9.4 | 22.8 | 0.1 | 0.3 | 24.9262 | 24.8527 | 285.2 | 35,255,000 |
| E (2–visit) | 68.8 | 99.0 | 9.4 | 22.8 | 1.1 | 1.3 | 24.9262 | 24.8527 | 283.2 | 34,884,000 |
| F (reflex) | 68.7 | 99.0 | 10.0 | 23.7 | 0.1 | 0.3 | 24.9262 | 24.8524 | 286.0 | 35,272,000 |
| F (2–visit) | 68.7 | 99.0 | 10.0 | 23.7 | 1.1 | 1.3 | 24.9262 | 24.8524 | 284.0 | 34,900,000 |
| G (reflex) | 68.2 | 99.0 | 6.6 | 19.5 | 0.1 | 0.3 | 24.9257 | 24.8502 | 282.8 | 35,145,000 |
| G (2–visit) | 68.2 | 99.0 | 6.6 | 19.5 | 1.1 | 1.3 | 24.9257 | 24.8502 | 280.8 | 34,774,000 |
| Liquid–based cytology | | | | | | | | | | |
| Classical | 71.7 | 98.9 | 17.5 | 32.6 | 1.4 | 1.7 | 24.9278 | 24.8623 | 321.5 | 39,990,000 |
| A | 72.1 | 99.4 | 13.0 | 27.6 | 0.9 | 1.1 | 24.9281 | 24.8634 | 318.3 | 39,931,000 |
| B | 72.1 | 99.4 | 22.1 | 37.3 | 0.7 | 1.0 | 24.9283 | 24.8638 | 323.5 | 40,118,000 |
| C | 71.7 | 99.4 | 12.3 | 26.5 | 0.7 | 1.0 | 24.9277 | 24.8618 | 315.5 | 39,766,000 |
| D | 72.2 | 99.1 | 16.8 | 30.0 | 0 | 0 | 24.9281 | 24.8636 | 317.0 | 39,213,000 |
| E | 71.8 | 99.1 | 10.7 | 24.3 | 0.1 | 0.3 | 24.9275 | 24.8620 | 313.5 | 39,384,000 |
| F | 71.8 | 99.1 | 11.5 | 25.4 | 0.1 | 0.3 | 24.9277 | 24.8620 | 314.5 | 39,399,000 |
| G | 71.3 | 99.0 | 7.7 | 21.1 | 0.1 | 0.3 | 24.9275 | 24.8605 | 310.3 | 39,257,000 |

[1]The management of BMD is follow–up with cytology and hrHPV testing (A–C), hrHPV testing at baseline and no follow–up (D), hrHPV testing at baseline and follow–up with cytology and hrHPV testing if hrHPV–positive (E–G). Baseline hrHPV testing can be performed by reflex testing (reflex) or by recalling women for a second visit (2–visit). Calculations are for conventional and liquid–based cytology in combination with GP5+/6+ PCR–EIA.–[2]In comparison to no screening.–[3]The screening summaries negative predictive value (NPV), colposcopy referral rate, and number of repeat smears were computed by averaging over cases with BMD at baseline. The negative predictive value was based on ≥CIN2 developed by the end of the 5–year screening round. Excessive colposcopies and follow–up smears (that do not lead to detection of ≥CIN2) were also separately tabulated.–[4]16,000,000 inhabitants. Costs consist of costs of cytological and hrHPV testing, colposcopy, and biopsy. Diagnosis costs made at follow–up visits to the gynecologist were not included.

Regarding the burden for women, the number of repeat smears always decreased with adjunct hrHPV testing. Moreover, a substantial reduction in the number of colposcopy referrals with outcome <CIN2 up to 52% could be achieved when repeating hrHPV-positive smears. The lifetime costs increased (range €0.2–€2.3 per woman) when the decision of colposcopy referral was based only on the baseline smear (strategies D reflex and D 2-visit) or on one repeat smear taken after 6 months (strategy B). The lifetime costs decreased for the other strategies with hrHPV testing (range €0.1–€5.3 per woman). Further inspection revealed that cost savings were caused mainly by a drop in the number of colposcopy referrals. Regarding strategies with baseline hrHPV testing (D–G), 2-visit hrHPV testing was cheaper than reflex hrHPV testing (difference in lifetime costs €2 per woman). Reflex testing would be relatively less expensive when the prevalence of BMD at baseline was higher or when the costs of co-collecting and transporting samples for reflex hrHPV testing were lower. In the model, reflex and 2-visit testing were equally expensive when either the baseline BMD prevalence was 5.3% or when reflex costs were €0.40 per smear.

We also did the calculations for HC2 instead of GP5+/6+ PCR-EIA. Similar results were obtained because the costs of strategies A–G increased by a maximum of only €0.40 per woman. We also estimated the annual nationwide diagnosis costs by summing the costs of cytology, the costs of hrHPV testing, and the costs of the first colposcopy and biopsy diagnosis after referral. In the Netherlands (population size about 16,000,000), each year 825,000 women are invited to screening.[52] In comparison to the classical strategy, the annual diagnosis costs increased by about €100,000 for strategies B, E reflex, and F reflex, decreased by at least €100,000 for strategies C, D 2-visit, E 2-visit, F 2-visit, and G 2-visit, and deviated less than €100,000 for strategies A, D reflex, and G reflex.

Finally, when considering all criteria in Table II simultaneously, strategies A, C, and E 2-visit performed particularly well. They outperformed the classical strategy on effectiveness (lower incidence of cancer and higher negative predictive value), burden (lower colposcopy referral rate and less repeat smears), and costs (lower lifetime costs per woman and lower annual nationwide diagnosis costs).

*Liquid-based cytology*

When liquid-based cytology was considered instead of conventional cytology, the reduction in cervical cancer incidence was 71.7% for the classical strategy (repeat cytological testing), which is 3.3% higher than that with conventional cytology. Except for strategy G (incidence reduction 71.3%), the incidence reductions were equally large or larger when combining liquid-based cytology with adjunct hrHPV testing. The maximum reduction (72.2%) was obtained when immediately referring women with an hrHPV-positive BMD smear for colposcopy (strategy D). The number of repeat smears were similar to those obtained with conventional cytology. The maximum reduction in the number of colposcopy referrals with outcome <CIN2 was 56% (strategy G).

Strategies with liquid-based cytology were more expensive than strategies with conventional cytology. The difference in lifetime costs was about €35 per woman and the difference in annual nationwide diagnosis costs was in the range of €4 to €5 million. Because hrHPV testing can be performed on the liquid-based specimen, cost savings achieved by adjunct hrHPV testing were somewhat higher when liquid-based cytology is the primary

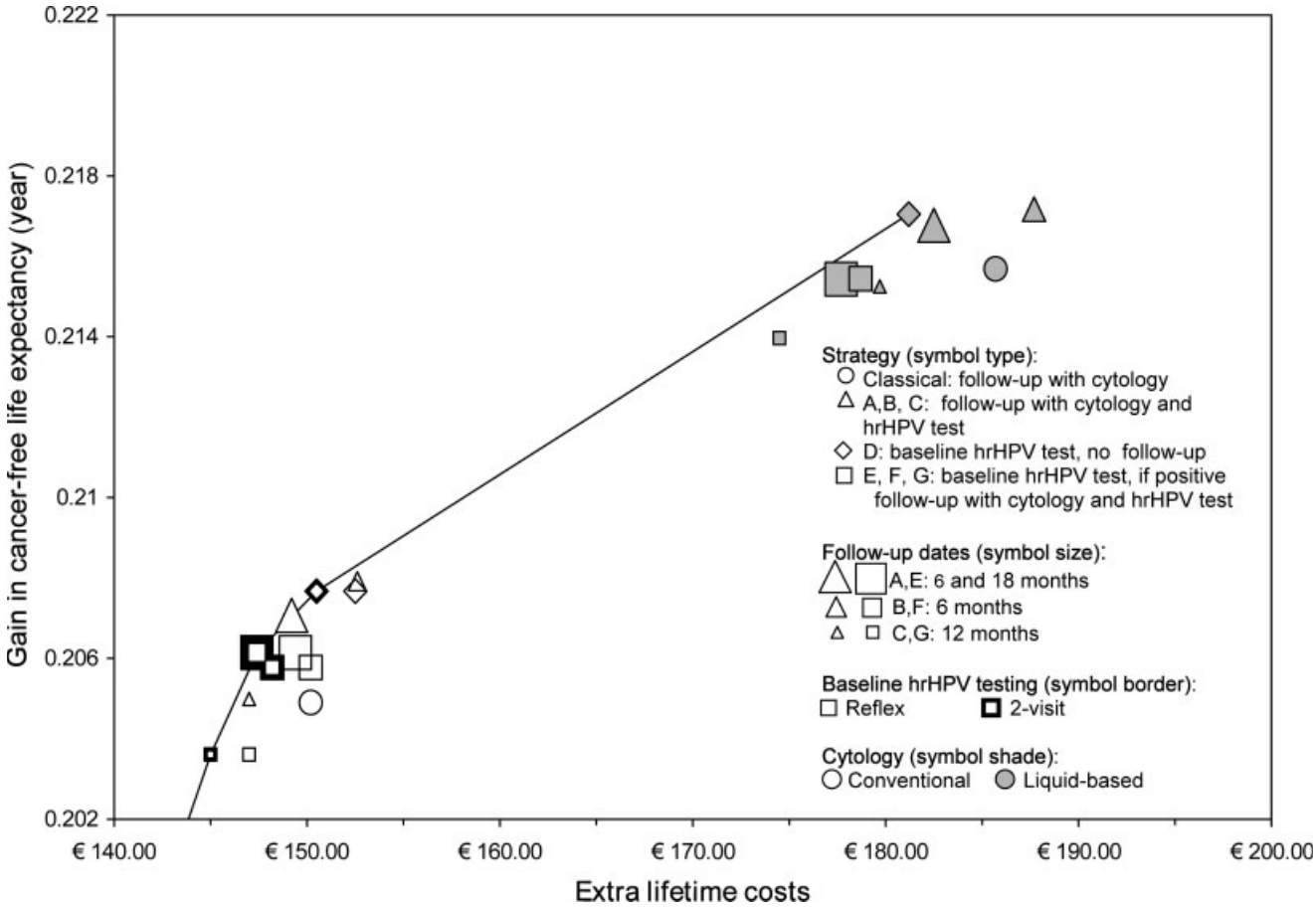


**FIGURE 2** – Cost-effectiveness plane and efficiency-frontier for classical strategy (repeat cytological testing with conventional or liquid-based Pap smear) and conventional or liquid-based cytological screening with adjunct GP5+/6+ PCR-EIA testing (strategies A–G). The costs and cancer-free life expectancy are expressed as incremental units in comparison to no screening. The discounting rate is 3% per year.

screening tool. Except strategy B for which the lifetime costs were €2.0 per woman higher than that for the classical strategy, the adjunct hrHPV testing strategies revealed cost savings ranging from €3.2 per woman (strategy A) to €11.2 per woman (strategy G). The changes in the annual nationwide diagnosis costs were in the same direction. In comparison to that of the classical strategy, the annual diagnosis costs increased €130,000 for strategy B. For the other strategies, cost savings ranged from €60,000 (strategy A) to €780,000 (strategyD).

*Cost-effectiveness*

The discounted overall and cancer-free life expectancy per woman are presented in Table I. In combination with conventional cytology, strategies A, D 2-visit, E reflex, E 2-visit, F reflex, and F 2-visit had lower lifetime costs and at least the same overall life expectancy as the classical strategy. In combination with liquid-based cytology, strategies A and D had lower lifetime costs and a higher overall life expectancy than the classical strategy. The discounted overall life expectancy for strategies with hrHPV testing and the life expectancy for the classical strategy did not deviate more than 0.0006 life-years. Because of the small differences, cost-effective strategies included strategy G, which was the least effective but also the least costly strategy (in combination with classical and liquid-based cytology). Liquid-based cytology was about €35 per woman more expensive than conventional cytology and led to a gain of 0.0016 in life expectancy. The incremental cost-effectiveness ratio of liquid-based screening (classical strategy) compared to conventional screening was about €22,000 per life-year saved per woman. By comparison, the incremental cost-effectiveness ratio of conventional cytology instead of no screening was about €3,000 per life-year saved per woman.

The effects of hrHPV testing became more pronounced when replacing the discounted life-years by the discounted cancer-free life years. The maximum difference in cancer-free life expectancy between hrHPV testing strategies and the classical strategy was 6 times higher than the difference in life expectancy. The gain in discounted cancer-free life expectancy is plotted against the discounted lifetime costs as shown in Figure 2, with cost calculations based on the cost price of GP5+/6+ PCR-EIA. Both for strategies with liquid-based and conventional cytology, some of the hrHPV testing strategies were more effective in terms of cancer-free life expectancy and less expensive than the classical strategy of repeat cytological testing. This indicates that the hrHPV test is a cost-effective adjunct screening tool, irrespective of whether primary screening is done with conventional or liquid-based cytology. For conventional cytological screening, strategies A, D 2-visit, E 2-visit, and G 2-visit were situated on the efficiency frontier as shown in Figure 2. For liquid-based screening, strategy D was on the efficiency frontier.

*Sensitivity analyses*

The effect of varying the analytical sensitivity of the hrHPV test on the incidence of cervical cancer reduction is presented for strategies A, D, and E (with conventional cytology) in Figure 3. The incidence reductions for strategies A and D were always higher than the one obtained for the classical strategy of repeat cytological testing. Strategy A appeared to be the most robust against a change in the analytical sensitivity of the hrHPV test as its curve (Fig. 3) was

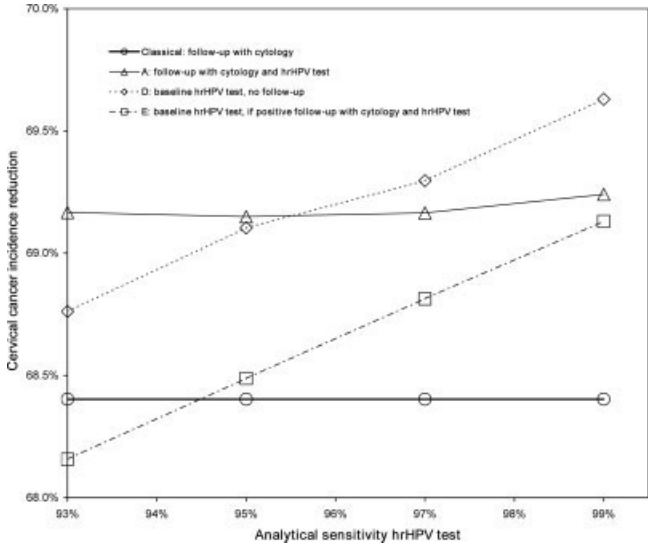


**FIGURE 3** – Reduction in incidence of cervical cancer compared to no screening against analytical sensitivity of hrHPV test.

nearly horizontal. Strategy E was only superior to the classical strategy when the analytical sensitivity of the hrHPV test exceeded 0.94 (an analytical sensitivity of 0.94 corresponds in the model to a clinical sensitivity for detecting CIN3 or worse of 0.86, which is lower than the clinical sensitivity reported in the literature[23,38]).

When the sensitivity of cytology was lowered to 40, 55, and 70% for thresholds CIN1, CIN2, and CIN3 respectively, the reduction in cervical cancer incidence became 63.2% for the classical strategy, 64.5% for strategies A and D, and 64.1% for strategy E. On the basis of a comparison of the base-case incidence reductions to the ones obtained after increasing (Table II: liquid-based cytology) and decreasing the sensitivity of cytology, we conclude that the increase in incidence reduction resulting from adjunct hrHPV testing is small but fairly robust against the sensitivity of cytology. When the screening interval was narrowed from 5 to 3 years, the reduction in cervical cancer incidences became 75.6% for the classical strategy, and 76.1%, 76.3%, and 75.9% for strategies A, D, and E respectively. Hence, the preventive effect of adjunct hrHPV testing was robust against narrowing the screening interval.

The cost-effectiveness results for adjunct hrHPV testing were robust against changes in the incidence of hrHPV infection, the CIN3 incidence, and the duration of CIN3 to FIGO stage 1 (results not shown). In Figure 4, the effects of screening characteristics and unit cost prices on the cost savings are presented for strategies A, D 2-visit, and E 2-visit (conventional cytology). Cost savings were robust against the specificity of the hrHPV test, the specificity of the repeat Pap smear, the length of the screening interval, the laboratory costs of hrHPV testing, and the costs of treating cervical cancer. Cost savings of strategy D 2-visit were moderately sensitive to the costs of treating a pre-invasive lesion. Cost savings were strongly sensitive to the specificity of cytology.

Although the sensitivity analyses were done for conventional cytology, the strong effect of the specificity of cytology on the costs is of particular interest for liquid-based cytology. The specificity of liquid-based cytology is less well documented than the specificity of conventional cytology and we assumed in the base-case model that the specificity of conventional and liquid-based cytology are equal. However, the increased sensitivity of liquid-based cytology may well come at the cost of a lower specificity. To examine the cost effect of a lower specificity, we decreased the specificity of liquid-based cytology by 1%. This led to an increase in the lifetime costs of €4.5 per woman and in the annual diagnosis and screening costs of €725,000. The hrHPV testing strategies turned out to be less sensitive to the specificity of cytology. For strategies A, D, and E, the lifetime costs increased by €3, €0.9, and €0.9 per woman and the annual diagnosis costs increased by €545,000, €185,000, and €185,000, respectively.

## Discussion

The hrHPV test is widely regarded as a sensitive instrument for cervical cancer screening, but the implementation of hrHPV testing in cervical screening is still under discussion and recommendations are sometimes conflicting.[53] We studied the use of the hrHPV test for the management of women with BMD smears by simulation modelling and found that adjunct hrHPV testing leads to a small decrease in the cervical cancer incidence and substantially lowers the burden for women, as measured by the number of repeat smears and referrals for colposcopy. The improvements can be achieved without increasing costs.

### *Effectiveness*

We carried out separate analyses for adjunct hrHPV testing in combination with conventional and liquid-based cytology. If combined with conventional cytology, all strategies with adjunct hrHPV testing yielded a larger negative predictive value for ≥CIN2 than the classical scenario of repeat cytology and all but one yielded a lower incidence of cervical cancer. The cervical cancer incidence reduction (compared to no screening) was 68.4% for repeat cytology and between 68.2% and 69.3% for strategies with hrHPV testing. The reason for the rather small difference in incidence reduction is that BMD smears constitute only 2.5% of the total amount of smears and only 5 to 15% of BMD is associated with an underlying high-grade lesion. In countries where the prevalence of BMD is considerably higher, a more pronounced change in the cervical cancer incidence is to be expected. In combination with liquid-based cytology, adjunct hrHPV testing still had a cancer preventive effect but because we assumed a higher sensitivity for liquid-based cytology than for conventional cytology, the difference in incidence reduction was smaller.

The strategies under consideration strongly differed with regard to the robustness against the sensitivity of the hrHPV test (Fig. 3). Not surprisingly, the robustness was rather low for strategies in which hrHPV-negative women at baseline were immediately sent back to routine screening. By contrast, the robustness was nearly perfect for strategies in which all women were included in the follow-up and were returned to routine screening only if the repeat smear was negative on both cytology and hrHPV. The latter strategy uses cytology as a safety net when the hrHPV test fails. Nonetheless, follow-up cohort studies indicate that the negative predictive value of an hrHPV-negative BMD smear is nearly 100%[7,9,10,28] and the clinical sensitivity for detecting CIN2/3 is about 95%[5,7,11,23] so that it seems safe to implement a strategy in which only baseline hrHPV-positive women are further examined.

### *Burden*

Compared to repeat cytological testing, adjunct hrHPV testing led to a decrease in the average number of repeat smears of at least 30% both for conventional and liquid-based cytology. By design, the reduction in the number of repeat smears is the largest when the hrHPV-test at baseline is decisive for either colposcopy or routine screening. Yet, we included strategies with follow-up for women who were hrHPV-positive at baseline to examine whether the colposcopy referral rate can be reduced. The rationale is that some women with an hrHPV-positive BMD smear show spontaneous regression in which case colposcopy referral is superfluous.[25] Compared to a conventional cytological screening strategy in which hrHPV-positive baseline smears were immediately referred for colposcopy, repeating hrHPV-positive women after 12 months led to a decrease of 52% in the number of colposcopy referrals with outcome <CIN2 but at the cost of a –1.1% (68.2% minus 69.3%) difference in cervical cancer incidence reduction. When repeating after 6 and 18 months, the corresponding percentages

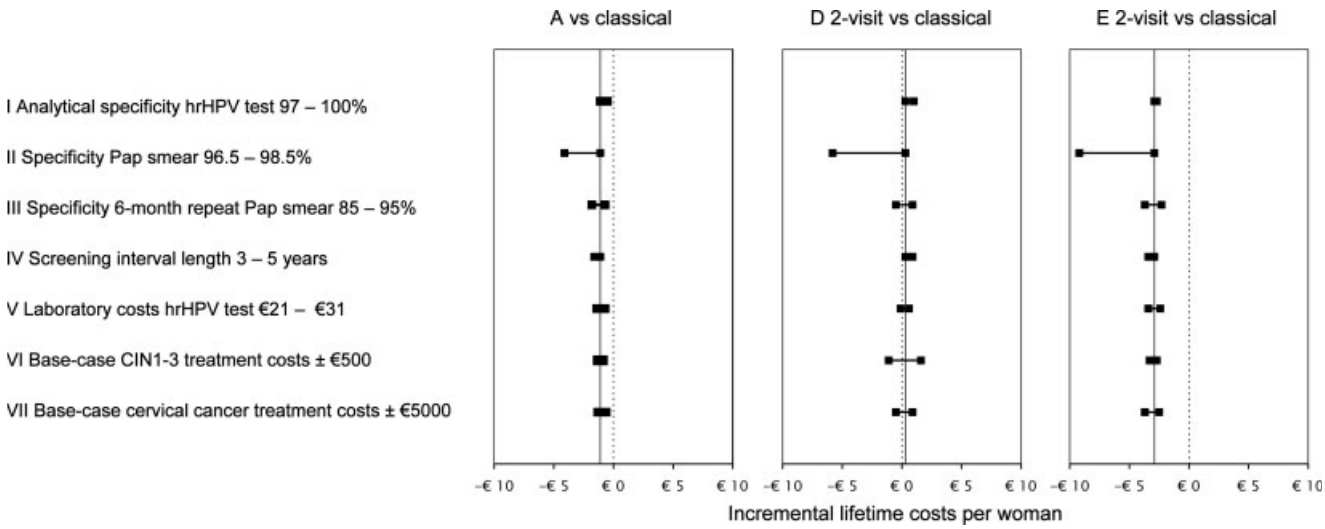


**Figure 4** – Extra lifetime costs per woman when using hrHPV testing along with conventional cytology (strategy A: follow-up with cytology and hrHPV test, D 2-visit: baseline hrHPV test within 1 month after BMD, no follow-up, and E 2-visit: baseline hrHPV test within 1 month after BMD, if positive follow-up with cytology and hrHPV test) instead of follow-up with cytology only (classical strategy). Future costs were discounted at 3% per year.

were 31 and –0.5. Hence, a longer interval to the first follow-up smear increases the risk of developing an invasive lesion and leads to an extra reduction in excessive colposcopy referrals of 21%. However, as cancer prevention weighs heavier than burden, we tend to favor strategies with either 2 or no repeat smears. In this regard, it should be noticed that our calculations are based on the assumption that all women with hrHPV-positive BMD attend follow-up screening. In case many women would be lost to follow-up, the strategy with no follow-up is the preferred one.

*Cost-effectiveness*

For cost-effectiveness calculations, one may either use overall life expectancy as a measure of effectiveness or as a measure that takes quality of life into account. When using overall life expectancy, which is commonly used in cervical screening models,[18,19] several hrHPV testing strategies were less costly and equally effective as repeat cytological testing although the effect of adjunct hrHPV testing on the life expectancy was very small. Overall life expectancy, however, is not a very sensitive outcome measure for assessing the effectiveness of screening for instance because women with cancer may still be cured and cancer can also be detected by symptoms rather than by screening. We found more pronounced effects of adjunct hrHPV testing when measuring the effectiveness by cancer-free life expectancy.

Liquid-based cytological screening led to a slightly higher life expectancy than conventional cytological screening, but our study was inconclusive with regard to the cost-effectiveness of liquid-based cytology. We computed that the costs of liquid-based screening were €22,000 per life-year saved in comparison with that of conventional screening. By comparison, the costs of conventional screening instead of no screening were computed to cost only €3000 per life year saved. However, the cost calculations relied heavily on the chosen cost price of evaluating a liquid-based Pap smear. In our model, the cost price of liquid-based Pap was €7 higher than the one of conventional Pap, but in other models,[18–20] the difference in cost price ranged between –€1 and +€10. The main factors to our estimated €7 increase are the price of the liquid-based Pap kit and the price of the slide preparation device. It is likely that the laboratory costs will trend downward because of large production of kits and the availability of fully automated technologies for preprocessing slides.[54] Moreover, savings on labor costs may be achieved since it takes less time to take and evaluate a liquid-based Pap smear than a conventional smear.[55] On the other hand, our sensitivity analyses showed that costs may be substantially higher when it turns out that the specificity of liquid-based cytology is lower than the one of conventional cytology.

In combination with conventional cytology, it was cost-effective to collect a sample for hrHPV testing at a second visit within 1 month or to postpone hrHPV testing to repeat smears taken at 6 and 18 months. With liquid-based cytology, it was cost-effective to apply reflex hrHPV testing at baseline from the liquid-based specimen. Strategies with reflex hrHPV testing were relatively expensive in combination with conventional cytology because then a sample for hrHPV testing at baseline has to be co-collected for the entire screening population as the cytological outcome is not yet known. The choice of the hrHPV test did not have a substantial effect on the cost calculations. Changing from G5+/6+ PCR-EIA to HC2 testing increased the unit cost price by maximum €5 per smear, but resulted in a lifetime cost increase of maximum €0.4 per woman.

*Extent and limitations*

The model used for the calculations was built on longitudinal information about hrHPV clearance and development and regression of CIN.[24] This makes the model suitable, especially, for evaluating the cost-effectiveness of screening strategies with repeat smears. The model outcomes compare well to recent independent cost-effectiveness predictions for the classical strategy of repeat cytological testing and the strategy of reflex hrHPV testing at baseline for equivocal smears reported in a study that involves multiple European countries.[56] In that study, the predicted costs in the Netherlands of repeat testing with conventional cytology in comparison to that of no screening were €3200 per life-year saved and the gain in life expectancy was .047. Our model predicted costs of €3000 per life-year saved and a gain in life expectancy of .05.

Although our model was estimated partly from data collected in the Netherlands and the current Dutch screening strategy was used as the baseline strategy, we believe that the results are representative for many other countries with nationwide screening. A strong point of the model is that the model parameters were validated against Dutch, British, and German population-based screening figures.[24] In addition, the model predictions turned out to be robust against changes in the progression parameters of the natural history model. The cost-effectiveness results also did not change

when narrowing the screening interval to 3 years. This is important as in many countries with population-based cervical cancer screening, the screening interval is either 3 or 5 years. Finally, in the model, the negative predictive value for ≥CIN2 was .991 when reflex hrHPV testing at baseline is decisive, .961 when one repeat conventional Pap smear after 6 months is decisive, and .969 when liquid-based Pap is used. Pooled negative predictive values reported in a recent meta-analysis[5] were .990 for reflex HC2 testing (8 studies) and .967 for repeat cytology (6 studies with conventional and 2 with liquid-based cytology). These arguments support that the recommendations made for the use of adjunct hrHPV testing have broad applicability.

The study design has some limitations. We confined ourselves to analyses where hrHPV testing is only used for the management of women with a BMD smear. However, hrHPV testing can also be used as a primary screening test. This leads to large extra screening costs that can possibly be countered by lengthening the screening interval. The latter problem was studied by some authors[17,18,20] who concluded that hrHPV testing on all baseline smears is cost-effective if the screening interval is somewhat lengthened. It remains to be investigated whether this type of strategy is cost-effective when the screening interval is 5 years. Another limitation is that we did not differentiate between borderline and mild dyskaryosis. In the Netherlands, the management is the same for the 2 cytological classes, but hrHPV-positivity is about 2 times higher for mild than for borderline dyskaryosis.[6] A call for separate management of borderline and mild dyskaryosis has already been made in the literature where in contrast to borderline dyskaryosis,[7,11,19] it was found by the ALTS group that the use of hrHPV testing in mild dyskaryosis (or LSIL) does not sufficiently lower the number of colposcopy referrals.[57] Nonetheless, recommendation for hrHPV testing in mild dyskaryosis depends on the hrHPV-positivity rate, which varies across countries. Therefore, it remains to be decided for which hrHPV positivity rate adjunct hrHPV testing is still cost-effective in mild dyskaryosis.

## Conclusion

This study provides valuable information for policy makers who evaluate the current guidelines for women with BMD. We showed that the addition of hrHPV testing to conventional or liquid-based cytology lowers the burden for women and leads to substantial cost savings in combination with a small reduction in the incidence of cervical cancer, depending on the strategy of first choice. Besides, we showed that liquid-based screening was somewhat more effective than conventional screening but also more costly. In combination with liquid-based cytology, it was cost-effective to perform reflex hrHPV testing after BMD at baseline from the liquid-based specimen. In combination with conventional cytology, reflex hrHPV testing is less easy to perform as a sample for hrHPV testing needs to be co-collected for the entire screening population. This leads to a substantial increase in screening costs, and it turned out to be more cost-effective to recall women with BMD within 1 month for hrHPV testing or after 6 and 18 months for hrHPV and cytological testing. In general, the cost benefits of hrHPV testing may be somewhat lower the first year as implementation costs have not been included in the calculations. However, the demand for extra capacity is limited because hrHPV testing would only involve women with BMD, that is, about 15,000 women each year in the Netherlands.

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