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Long-term costs of introducing HPV-DNA post-treatment surveillance to national cervical cancer screening in Ireland

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Abstract

Introduction—Co-testing (cytology plus human papillomavirus DNA testing) as part of cervical cancer surveillance in Ireland increases one-time testing costs. Of interest to policy makers was the long-term impact of these costs accompanied by decreases in intensity of recalls for women with no detected abnormalities.

Methods—A cost-analysis of cytology-only and co-testing was implemented using decision analytic modeling, aggregating testing utilization and costs for each of the two strategies over 12 years.

Results—Aggregated incremental costs of the co-testing strategy were positive for the first 3 years but became negative thereafter, generating a cost savings of roughly €20 million in favor of the cytology-only strategy over a 12-year period. Results were robust over a range of sensitivity analyses with respect to discount and attrition rates.

Discussion—This analysis provided valuable information to policy makers contributing to the introduction of co-testing for post-treatment surveillance in Ireland.

Keywords

Post-treatment surveillance; human papillomavirus; cervical cancer; colposcopy; costs analysis; screening; decision analysis

Introduction

Objective

Women with a history of high grade cervical intraepithelial neoplasia (CIN) face a significant risk of developing post treatment disease [1]. Thus, post-treatment surveillance

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(PTS) features in many European countries' screening programmes [2] but follow-up frequency and duration varies greatly within and between countries [3,4]. Previously in Ireland, cytology-only was recommended at 6 months post-treatment, then at 18 months and annually, for 5-10 years thereafter [5]. In 2012, CervicalCheck—The National Cervical Screening Programme in Ireland—adopted a new PTS strategy of human papillomavirus (HPV) and cytology co-testing following colposcopy treatment. In this study, we present results from a cost-analysis, comparing a HPV-cytology based (co-testing) strategy to a cytology-alone based strategy.

This work arose following the establishment of a National Cancer Screening Service (NCSS) Scientific Advisory Group to review the evidence and make recommendations regarding the use of HPV testing in surveillance of women following treatment at colposcopy. To help inform the deliberations of the Group and the decision of NCSS in respect to the adoption of HPV-testing a cost-analysis was requested as part of the evidence to be considered by the NCSS. The importance of undertaking a cost-analysis was underscored by the financial crisis which overtook Ireland in 2008 and the introduction of austerity measures across all services in the public sector. NCSS requested the analysis and agreed to supply such data as were available to support its conduct as detailed below. The research team was comprised of the authors of this report, two of whom were employed by the NCSS (AS and AD), one of whom chaired the Scientific Advisory Panel (CON). NCSS also helped inform discussions regarding aspects of the sensitivity analyses with respect to the range over which parameter inputs might vary. The NCSS coauthors collaborated with academic researchers in Ireland (CO) and the USA (MA and AB) in order to carry out the analysis.

We begin the report with a brief background on the epidemiology of cervical cancer, population cancer screening, including the use of HPV testing in Ireland. We discuss the clinical and economic impacts of post-treatment surveillance. Then, we present, in five parts, the design of the cost-analysis: (1) analytical framework, (2) perspective and time horizon, (3) treated population, (4) input costs and data sources, and (5) sensitivity analyses [6]. Lastly, we present results, discuss policy implications and limitations of the analysis.

Epidemiology and surveillance of Cancer of the Cervix in Ireland

Cancer of the cervix is the second most common cause of cancer in women and the sixth most common cause of cancer overall [7]. In Ireland, although incidence of primary cervical cancer has been reported [8,9], little is known about recurrence incidence rates [10]. A study from the Netherlands found that incidence of cervical cancer in post-treatment women was 35 in 100,000 person years, a four-fold increase compared to the population testing repeatedly negative in primary screening [3]. More importantly, even less is known about effectiveness of PTS in Ireland and in other countries. A systematic review of randomised controlled trials (RCTs) attempted to compare different follow-up cervical cancer PTS protocols but concluded that no available evidence exists [4].

In Ireland, cervical screening began in what was the former Mid Western Health Board Region in 2000. This was a pilot phase during which key operational issues were prepared and tested before the implementation of a full national programme. Other policy

developments that impacted the strategic and operational direction of the programme included the launch of 'A Strategy for Cancer Control in Ireland 2006' and the formal establishment of the NCSS in 2007. It was at this time that the governance of cervical screening transferred to the then Board of the NCSS. The NCSS then launched CervicalCheck – The National Cervical Screening Programme in 2008. CervicalCheck is a quality assured, organised and population-based screening programme that provides free cervical screening (smear tests) to residents in the Republic of Ireland, aged 25 to 60. Post-treatment surveillance for women with abnormal smears requiring an excisional treatment in colposcopy is a component part of the CervicalCheck programme.

The NCSS reported in 2009, that CervicalCheck screened 300,000 women and cost 43.12 million € incorporating cytology screening, colposcopy treatment and post treatment surveillance. This compares with a cost in the UK of 175.95 million € for similar services to 3.8 million women. The average cost per woman in the UK was 45.95 € compared to an average cost per woman screened in Ireland of 144 € [11]. This variation in costs played a role in the effort to identify cost-saving policy changes for the CervicalCheck programme.

Clinical impact of post-treatment surveillance

PTS has traditionally involved intensive cytological (smear) tests at semi-annual, then annual intervals for as long as 12 years. The limitations of cytology-only based strategy, however, have come to be increasingly recognised. For example, the relatively low sensitivity of a single smear test to detect high-grade precursor lesions requires frequent testing if post-treatment surveillance using cytology is to be effective [12]. Not only is this expensive but it can give rise to a large number of false positives over time with the additional attendant investigation costs [13] as well as anxiety for the women concerned. In addition, the fall in cytology-detected cancer incidence appears to be largely confined to squamous cell carcinoma and suggests cytology-only based strategies may be less effective at detecting adenocarcinomas and its precursors [14,15].

An increasing body of evidence has emerged to indicate that HPV testing can predict treatment failure with significantly higher sensitivity and similar specificity compared to repeat cytology [10,16,17]. More recent studies also point to the added predictive value of co-testing, HPV testing undertaken in conjunction with cytology [3,18]. There is evidence to support post-treatment women safely returning to the less-intensive normal screening recall schedule after consecutive 6 and 18-month negative co-testing results [19].

Economic Impact of post-treatment surveillance

Modeling long-term costs provides valuable information to health service planners whose budgets may be directly affected as a result of a policy change. Using the underlying assumption that HPV testing is at least as effective as cytology in our specific setting, we focused on the potential financial impact of the adoption and diffusion of a new technology or intervention on the health-payer's budget. The analysis described below was undertaken in a manner consistent with guidance issued by the Health Information and Quality Authority (HIQA) the statutory body with responsibility for providing guidance on such matters in Ireland [20].

Methods

Model Analytical Framework

We used decision analytic methods to calculate long-term costs of two cervical cancer recurrence PTS strategies. Using patterns of CervicalCheck service evident at the time (supplied by NCSS, 2010), the model assumes that the service screens approximately 334,180 women each year. Of these approximately 5% (16,709) are referred to colposcopy. Of these 51% (8,522) will receive an excisional treatment and then become eligible for PTS. Thus, we aggregated costs of an annual hypothetical cohort of 8,522 women transitioning through the cytology-only and the co-testing PTS strategies (Fig.1). We performed analyses using TreeAge Software 2009 (Williamstown, MA) [21].

Perspective and time horizon

We calculated net costs, from the NCSS perspective, using Markov chain processes with 1 year intervals and a 12 year time horizon.

Treated Population

Under the cytology-only PTS strategy women with high grade CIN (CIN 2/3) were followed up for 18 months in the colposcopy clinic, receiving a smear between 6 and 12 months after initial treatment. Women whose follow-up cytology was negative (including endocervical cells) were then transferred to primary care where they would under normal circumstances be followed up with annual smears for another 10 years. For example, in year 1, 8,522 enter PTS. In year 2 (18 months post treatment) 98.5% of these women (8,394) are referred to primary care for annual follow-up; the model does not track the remaining 1.5% with abnormal HPV and or cytology who undergo further treatment (Fig. 1a). In each subsequent year new cohorts of women are added to the original 8,522 seen in colposcopy of which 8,394 are added to the reservoir of predecessors in primary care. The numbers of women in primary care follow up build incrementally until year 12 at which point the numbers being added to PTS equal those exiting to primary care follow-up. The cohorts of women who do not complete PTS (e.g. cohort entering at year 11) at the end of the 12 year time horizon are not further followed in the model.

The HPV and cytology PTS strategy (co-testing) also involves cytology at 6 months after treatment, performed in the colposcopy clinic (Fig. 1b). However, an HPV test is performed alongside cytology. A repeat smear and HPV test are then performed, 18 months after initial treatment, again in the colposcopy clinic. Women with abnormal HPV results are referred to the annual PTS cytology-only recall but referral for colposcopy procedure is based on abnormal findings in cytology. The percentages reported in Figures 1a and b are based on a combination of numbers observed in the current system and outcomes from a Scottish pilot of co-testing [22].

Transition to Routine Recall

Routine recall refers to the Cervical Check screening interval: triennial screening if between ages 25-44 years old and screening every five years if between the ages of 45-60 years old. We did not model routine recall in the cytology-only PTS strategy because women must test

negative in 2 semi-annual and 10 annual recalls before returning to routine recall, accounting for all 12 years of the model time horizon. In the co-testing PTS strategy, women return to routine recall after testing normal in 2 semi-annual follow-up HPV and cytology tests. For simplicity, age was not considered in the model.

Input Costs and Data Sources

Procedures, by visit type, were provided by the NCSS (Table 1). The costs of the cytology-only strategy including consumables – smear test and speculum - and reimbursement to service providers for laboratory costs, collectively amount to €38.98 for each test. In primary care at that time, an additional fee of €1.69 was paid to the primary care provider. In addition to the unit costs detailed above, the co-testing PTS strategy includes a laboratory HPV test fee paid to the relevant service providers. To investigate a hypothetical threshold cost of the test at which point the cytology-only and co-testing strategy costs were equal we performed a threshold analysis. A four percent discount was applied to costs in years 2-12 of the analysis.

Capital costs are assumed to be constant and identical for both PTS strategies while all overheads – heat, light power, administration etc.—are assumed to be embedded with the reimbursement fees paid for services rendered. Separate consideration of capital and overhead costs are not therefore pertinent to comparisons between the two strategies. Because this analysis is takes the perspective of NCSS, only costs associated with transitioning through the two PTS strategies are considered. Thus, downstream costs of diagnosis and treatment are not included in the calculations.

Sensitivity Analyses

We investigated the effect of attrition on long term costs by modelling a 10%-20% drop out of women after the initial 6 month follow-up after treatment visit. To see the impact of marginal false positive results attributable to HPV testing, we increased in the co-testing strategy the number of women referred for further follow up. Although this analysis aggregates follow-up test costs and excludes diagnosis or treatment costs, women with a positive HPV result move to the conventional annual recall, a more resource intensive schedule than the triennial screening interval. Lastly, using Monte Carlo Markov Chain simulation of 10,000 iterations we performed probabilistic sensitivity analysis to evaluate the simultaneous impact on long term costs of dramatically varying costs and modestly varying transition probabilities. We assumed costs were gamma distributed (standard deviation equal to the mean) and transition probabilities were beta distributed (integer form, assuming the population size is 100 and the number of occurrence is equal to the transition probability of interest).

Results

The total costs and difference in total costs with each PTS strategy under four separate scenarios are presented in Table 2. The base case scenario is presented as analysis 1. In this analysis the net savings are greatest (just under €20 million). Although discounting of future costs is unnecessary for completeness, in analysis 2 we show that discounted costs bring the

two PTS strategies closer together in terms of costs. To model a common occurrence of attrition in PTS, in analysis 3, we applied 15% attrition to each strategy after the initial 6 month follow up. Naturally, drop-out of a more expensive approach will proportionally drive down costs of the cytology-only PTS strategy decreasing further the net savings of the co-testing strategy. In the fourth scenario analysis we explored the impact of higher false positives from HPV testing (3-fold the base case scenario) on costs of the co-testing strategy and found that adding HPV testing to the PTS schedule still leads to cost-savings, albeit smaller in magnitude.

Over a twelve year span, the co-testing PTS strategy results in net costs for the first two years of its operation – associated with the addition to current practice of the HPV test – but thereafter each year net savings are incurred (Fig. 2). When the two PTS strategies reach “steady state” (the number of women entering PTS equals the number exiting), the co-testing PTS strategy supports a net saving of €3.2 million per year. The undiscounted aggregate net savings over twelve years is just below €20 million. Results of the threshold analysis revealed that the maximum cost of the HPV test has to reach €34.53 before the co-testing PTS strategy breaks even with the cytology-only PTS strategy. This value far exceeds the true, but proprietary, cost of implementing the HPV test in colposcopy clinics.

We also performed probabilistic sensitivity analysis by simultaneously drawing random values from the distributions assigned to variables in the model (Table 1). These results are depicted graphically using a cloud diagram (Figure 3). The dotted grey line depicts net difference of zero between the two PTS strategies. The steeper black trend line indicates that the cytology-only PTS strategy, on average incurs higher costs than the co-testing strategy. In 76.3% of the 10,000 simulations, the co-testing PTS strategy is less costly.

Discussion

Early detection of cervical cancer recurrence, given the likelihood of recurrence of high grade CIN, requires a well-designed and highly sensitive PTS strategy. The low sensitivity of a single smear test to detect high grade lesions is well documented and is the basis for intense follow-up surveillance based on cytology alone. A consensus around the superiority of HPV-based tests in prevention is emerging [23] and affords an opportunity for less intensive follow-up of women post-treatment. Our analysis is based on data taken from a national service provider and a pilot study of HPV-based testing used in conjunction with cytology. Our study clearly demonstrates a significant and positive budget impact may accompany a shift away from PTS based on cytology alone. Savings of over €3 million per year are indicated when the PTS strategy of combined HPV and cytology reaches steady state. Our finding that a PTS strategy incorporating HPV-based testing allowed for less intensive follow-up remained robust over a range of sensitivity analyses and adds weight to the clinical arguments for a change in the approach to PTS.

Our analysis required a number of simplifying assumptions (Table 3). Effectiveness in this analysis was assumed to be equal between the cytology-only and co-testing PTS strategies. Evidence suggests that HPV testing improves sensitivity translating to earlier detection and intervention. This model does not account for any cost-savings or superior outcomes

associated with improved effectiveness. However, an economic evaluation of HPV testing in the English post-treatment population has shown when compared to long-term cytology-only, HPV surveillance is both more effective and cost-saving [24].

There is no longitudinal data of compliance to these different PTS strategies. Although we expect differential attrition rates with each approach, it is difficult to predict which will favour better compliance. Frequent follow-up associated with a cytology-alone based approach may well have higher attrition rates. While attrition may produce “savings” in PTS costs, given its implications for women's health it can hardly be judged to present an indication of success of cytology-only PTS strategy. Conversely, women may be more suspicious of repeating a test associated with sexually transmitted diseases and attrition may be differentially higher in the co-testing PTS strategy, in turn increasing the net savings of the co-testing strategy. In either case, savings from attrition are potentially counter-balanced by the additional costs associated with later detection and treatment of those women whose drop-out results in delayed cancer detection. As this takes us into the realm of evaluation, however, and away from direct costs to CervicalCheck, we have chosen not to speculate on this. In sensitivity analysis we showed that the co-testing PTS strategy remains cost-saving under non-differential and low-levels of differential attrition rates.

In this analysis we did not account for impacts on the budget from referrals for diagnosis and treatment. It is quite likely that differences in downstream interventions exist but these costs would not accrue to CervicalCheck and thus are not relevant to this analysis. We did not explicitly address decreases in specificity arising from co-testing with HPV when compared to cytology alone[10]. In the co-testing PTS strategy, a woman with abnormal results by either HPV or cytology enters annual cytology PTS. To account for this we performed sensitivity analysis, increasing the number of women, by 3-fold, entering annual cytology PTS in the co-testing PTS strategy (Table 2). Incident HPV+ result in 42% of the cohort and 33% of the cohort, at 6- and 18-month follow up respectively, transitioning to the more frequent annual cytology PTS. We show that cost-savings of the co-testing PTS strategy diminish by EUR 7,844 but the co-testing PTS strategy remains cost-saving. Analysis 4 represents a worst-case scenario. Thus, we can expect true cost-savings to CervicalCheck to be between that reported in analyses 2 and 4 (Table 2).

The model similarly excludes downward changes in treatment costs expected in the PTS strategy with superior effectiveness.

We assumed that capital costs in the two PTS strategies are identical. In practice capital costs may differ though it is difficult to imagine these differing to an extent that would materially impact on the conclusion of the study.

Our analysis helped affirm the decision of the NCSS to move from PTS based on cytology-alone to one based on HPV testing in conjunction with cytology. It demonstrates the usefulness of cost modelling to inform policy decisions quickly and effectively.

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References

1. Soutter WP, Sasieni P, Panoskaltsis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. *Int J Cancer*. 2006; 118(8):2048–2055. [PubMed: 16284947]
2. Health Professionals. [Last accessed February 21 2012] CervicalCheck: The National Healthcare Screening Programme. Available at: <http://www.cervicalcheck.ie/health-professionals/about-the-programme.149.html>
3. Rebolj M, Helmerhorst T, Habbema D, et al. Risk of cervical cancer after completed post-treatment follow-up of cervical intraepithelial neoplasia: population based cohort study. *Bmj*. 2012; 345:e6855. [PubMed: 23117059]
4. Lanceley A, Fiander A, McCormack M, Bryant A. Follow-up protocols for women with cervical cancer after primary treatment. *Cochrane Database Syst Rev*. 2013; 11:CD008767.
5. Khalid S, Carcopino X, Michail G, Metchette S, Conroy R, Prendiville W. Compliance with Follow up Cytology after Discharge from the Colposcopy Clinic. *The Irish Medical Journal*. 2015; 108(4)
6. Sullivan SD, Mauskopf JA, Augustovski F, et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. *Value Health*. 2014; 17(1):5–14. [PubMed: 24438712]
7. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer*. 2013; 132(5):1133–1145. [PubMed: 22752881]
8. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: 2012. Available at: <http://globocan.iarc.fr> [Last accessed January 12 2014]
9. National Cancer Registry Ireland. [Last accessed January 12 2014] Cancer Factsheet: Cervix. 2013. Available at: http://www.ncri.ie/sites/ncri/files/factsheets/FACTSHEET_cervix.pdf
10. Kocken M, Uijterwaal MH, de Vries AL, et al. High-risk human papillomavirus testing versus cytology in predicting post-treatment disease in women treated for high-grade cervical disease: a systematic review and meta-analysis. *Gynecol Oncol*. 2012; 125(2):500–507. [PubMed: 22266548]
11. Health Information and Quality Authority. [Last accessed May 15 2015] Report of the evaluation of the use of resources in the national population based cancer screening programmes and associated services; Cork. p. 2009 Available at: http://www.hiqa.ie/system/files/Colorectal_cancer_evaluation_report_HTA.pdf
12. Cuzick J, Clavel C, Petry KU, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer*. 2006; 119(5):1095–1101. [PubMed: 16586444]
13. Katki HA, Wentzensen N. How might HPV testing be integrated into cervical screening? *Lancet Oncol*. 2012; 13(1):8–10. [PubMed: 22177578]
14. Bulk S, Visser O, Rozendaal L, Verheijen RH, Meijer CJ. Cervical cancer in the Netherlands 1989-1998: Decrease of squamous cell carcinoma in older women, increase of adenocarcinoma in younger women. *Int J Cancer*. 2005; 113(6):1005–1009. [PubMed: 15515017]
15. Vahidnia F, Hirschler NV, Agapova M, Chinn A, Busch MP, Custer B. Cancer Incidence and Mortality in a Cohort of US Blood Donors: A 20-Year Study. *J Cancer Epidemiol*. 2013; 814842 2013.

16. Zielinski GD, Rozendaal L, Voorhorst FJ, et al. HPV testing can reduce the number of follow-up visits in women treated for cervical intraepithelial neoplasia grade 3. *Gynecol Oncol*. 2003; 91(1): 67–73. [PubMed: 14529664]
17. 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(3):S3/78–89.
18. Uijterwaal MH, Kocken M, Berkhof J, et al. Posttreatment Assessment of Women at Risk of Developing High-Grade Cervical Disease: Proposal for New Guidelines Based on Data From The Netherlands. *J Low Genit Tract Dis*. 2014
19. Kocken M, Helmerhorst TJ, Berkhof J, et al. Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: a long-term multi-cohort study. *The Lancet Oncology*. 2011; 12(5):441–450. [PubMed: 21530398]
20. Health Information and Quality Authority. [Last accessed May 15 2015] Guidelines for the Budget Impact Analysis of Health Technologies in Ireland. Health Information and Quality Authority. Cork. 2010. Available at: <http://www.hiqa.ie/publications/guidelines-budget-impact-analysis-health-technologies-ireland>
21. TreeAge Software Inc. TreeAge Pro 2009. Williamstown, MA: 2009. Ed. ^ Eds
22. Cubie HA, Canham M, Moore C, Pedraza J, Graham C, Cuschieri K. Evaluation of commercial HPV assays in the context of post-treatment follow-up: Scottish Test of Cure Study (STOCS-H). *J Clin Pathol*. 2014; 67(6):458–463. [PubMed: 24436334]
23. Jordan J, Martin-Hirsch P, Arbyn M, et al. European guidelines for clinical management of abnormal cervical cytology, part 2. *Cytopathology*. 2009; 20(1):5–16. [PubMed: 19133067]
24. Legood R, Smith M, Lew JB, et al. Cost effectiveness of human papillomavirus test of cure after treatment for cervical intraepithelial neoplasia in England: economic analysis from NHS Sentinel Sites Study. *Bmj*. 2012; 345:e7086. [PubMed: 23117060]

Key Issues

- The probability of disease recurrence in treatment of women with high grade CIN requires PTS as part of an effective national cervical cancer screening programme.
- The limitations of a cytology-alone based PTS strategy, necessitates a more intensive follow up of treated women than a strategy that uses both HPV and cytology.
- Our analysis shows significant potential savings may arise for the budget holder associated with the less intensive post treatment surveillance of women. The results of this analysis strengthened the case for the incorporation of HPV testing as part of the continued evolution of CervicalCheck – The National Cervical Screening Programme.
- The NCSS presented the clinical, scientific and cost analyses to the Department of Health (Ireland) and ultimately HPV testing in the post colposcopy treatment setting alongside the less intensive use of cytology modelled in this analysis was incorporated into the national screening programme in 2012.

Figure 1. a-b. PTS strategies presented as transition states

1a. Follow up testing transitions in the cytology-only strategy.

1b. Follow up transitions in the co-testing schedule. Conventional annual recall: enter annual cytology PTS. Triennial schedule: return to routine recall screening.

*At each transition some women will exit the PTS schedule to undergo diagnosis, treatment or be lost to follow up. In the analysis, women confirmed negative by colposcopy are assumed not to re-enter PTS.

Figure 2. Annual Costs by PTS Strategy and Cumulative Cost Savings

Figure 3. Probabilistic sensitivity analysis: Monte Carlo Simulation of Costs of Each Strategy over 12 years

Table 1
PTS costs and transition probabilities

Type of visit	Costs (€)	Distributions
Colposcopy clinic (cytology-only strategy)	38.98	Gamma (1, 1,521)
Colposcopy clinic (co-testing strategy)	78.31	Gamma(1, 6,241)
Primary care visit	90.67	Gamma(1, 8,281)
Transition probabilities of the cytology-only strategy	Probabilities	Distributions
Transition to GP from 6 month check up	99%	Beta(100,1)
Transition probabilities of the co-testing strategy	Probabilities	Distributions
Transition to GP from 6 month check up	14%	Beta(100, 86)
Transition to 2yr follow up in colposcopy clinic	85%	Beta(100, 15)
Transition from 2yr follow up to conventional annual recall	11%	Beta(100, 89)

Table 2
Results as costs and cost differences of the cytology-only and co-testing PTS strategies

Analyses		12 Year Costs (€1,000s)		
		Cytology-only strategy	Co-testing strategy	Cost Difference
1	Base case (no discount, no attrition)	EUR 53,455	EUR 33,494	EUR 19,961
2	Discount (4%), no attrition	EUR 38,601	EUR 24,603	EUR 13,997
3	Discount (4%), 15% attrition after initial 6 month follow up	EUR 33,278	EUR 22,582	EUR 10,696
4	Discount (4%), 3-fold increase in positive HPV/cytology at 6 month and 18 month follow up	EUR 38,601	EUR 32,088	EUR 6,513

Table 3
Model assumptions

Assumptions		
1	Non-inferior effectiveness	In the setting of surveillance, HPV testing +cytology at reduced frequency is at least as effective as annual cytology alone
2	Similar downstream costs	Decreased HPV specificity does not lead to significant increases in referrals for diagnosis and treatment and associated costs to the payer
3	Non-differential attrition rates	Women are no more or less likely to return for scheduled follow-up after adding the HPV test and reducing frequency of follow-up
4	Negligible capital costs	Capital costs required to implement the co-testing strategy (e.g. personnel, equipment and supplies), spread across 12 years, are negligible