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Cost-effectiveness of using human papillomavirus 16/18 genotype triage in cervical cancer screening ☆

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ABSTRACT

Objective. Testing for human papillomavirus (HPV) 16 and 18 genotypes, which are known to cause approximately 65–70% of invasive cervical cancer cases, may allow clinicians to identify women at highest risk for underlying cervical intraepithelial neoplasia missed by Pap cytology. Our objective was to determine the cost-effectiveness of adding HPV-16 and 18 genotype triage to current cervical cancer screening strategies in the United States.

Methods. We developed a lifetime Markov model to assess the cost-effectiveness of the following cervical cancer screening algorithms: (1) liquid-based cytology (LBC), (2) LBC + HPV triage, (3) HPV + LBC triage, (4) co-screening, (5) co-screening + HPV genotyping, and (6) HPV only + HPV genotyping. Costs were estimated from a payer perspective in 2007 U.S. dollars. Outcome measures included lifetime risk of cervical cancer, quality-adjusted life years saved (QALYs), and incremental cost-effectiveness ratios (ICERs).

Results. In our model, the use of HPV genotyping strategies prevented 51–73 deaths per 100,000 women screened compared to screening using LBC followed by HPV triage and 4–26 deaths compared to co-screening with LBC and high-risk HPV. Use of HPV genotyping to triage all high-risk HPV-positive women every three years had an ICER of $34,074 per QALY compared to HPV and LBC co-screening. HPV genotyping with co-screening was the most effective strategy and had an ICER of $33,807 per QALY compared to HPV genotyping for all high-risk HPV-positive women.

Conclusion. The addition of HPV-16 and -18 genotype triage to HPV and LBC co-screening was a cost-effective screening strategy in the United States.

Introduction

Virtually all cases of cervical cancer are caused by persistent infection with specific high-risk types of human papillomavirus (HPV). The most common HPV genotypes detected in invasive cancers are HPV type 16 (HPV-16) and HPV-18, which are present in approximately 65–70% of invasive cervical cancer cases [1,2]. HPV genotyping tests that screen for specific types of high-risk HPV recently received FDA approval and can be used for primary screening in women 30 years and older in conjunction with high-risk HPV DNA tests and cervical cytology or in combination with high-risk HPV DNA tests to triage women with a cytology result of atypical squamous cells of undetermined significance (ASCUS) [3].

HPV DNA testing is considerably more sensitive than cytology at detecting high-grade cervical intraepithelial neoplasia (CIN) [4–6] but is less specific due to the detection of transient HPV infections that may not progress to cervical lesions [7]. Using HPV genotyping to triage HPV-positive women may increase the specificity of HPV DNA testing thereby reducing referrals for colposcopies and treatment while still maintaining a high sensitivity [7,8].

The cost-effectiveness of using HPV genotyping tests has not been established. The purpose of our study was to determine the cost-effectiveness of adding HPV-16 and -18 genotype triage to current cervical cancer screening strategies in the United States.

Materials and methods

We developed a lifetime Markov Monte Carlo model to assess the cost-effectiveness of adding HPV genotyping tests to current cervical cancer screening algorithms [9,10]. In a Markov model, uncertain events are modeled as transitions between health states. As such, we modeled the natural history of cervical neoplasia using 18 distinct Markov health states representing type-specific HPV infection, CIN, and invasive cervical cancer (Fig. 1). Women could transition between

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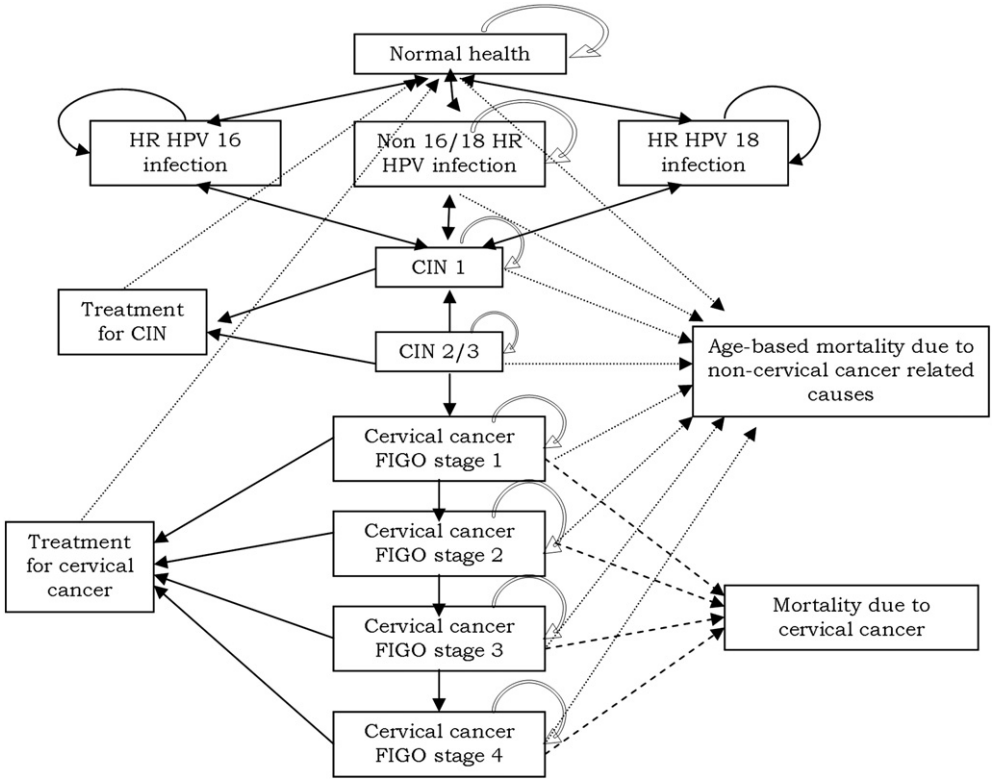

Fig. 1. Schematic representation of the model. HR HPV denotes high-risk human papillomavirus, CIN cervical intraepithelial neoplasia, and FIGO International Federation of Gynecology and Obstetrics.

health states at the end of each month. The natural history of HPV infection, CIN, and cervical cancer was based on data from the published literature and the incidence of disease varied with age (Table 1) [1,2,12–24]. The Monte Carlo simulation, a computational method based on repeated random sampling, was used to evaluate the model for a hypothetical cohort of 100,000 U.S. women over their lifetimes, starting at age 13 years. All modeling was conducted using TreeAge Pro 2007 release 1.5 (TreeAge Software, Williamstown, MA). Detailed methods regarding our core cervical cancer screening model have been published previously [11].

We assumed that all women would undergo biennial liquid-based cytology (LBC) testing until age 30. After age 30, we compared the following screening strategies (refer to Supplemental digital content S1 for detailed screening algorithms):

- Screening using LBC every two years (LBC);
- Screening using LBC every two years, followed by HPV DNA testing for all patients with equivocal results on cytology (ASCUS) (LBC + HPV triage);
- Primary screening using HPV DNA testing every three years, followed by cytology for all women with positive result on HPV (HPV + LBC triage);
- Screening using a combination of simultaneous cytology and HPV DNA testing every three years (co-screening);
- Screening using a combination of simultaneous cytology and HPV DNA testing every three years, with reflex HPV genotyping and more intensive follow-up for HPV types 16/18 (co-screening + HPV genotyping);
- Screening using HPV DNA testing every three years, followed by reflex HPV genotyping for all HPV-positive women and more intensive follow-up for HPV types 16/18 (HPV only + HPV genotyping).

Screening and treatment protocols were based on recently published consensus guidelines [25,26]. The sensitivity and specificity of the LBC and standard HPV tests were based on clinical studies and meta-analyses in the published literature [18–20]. In the genotyping strategies, we assumed that patients who have normal cytology, a positive HPV result, and are HPV-16 or -18 positive will receive immediate colposcopy and biopsy, while those who are HPV-16 and -18 negative will have repeat LBC and HPV tests in one year [3].

Costs were estimated from a payer perspective, and unit costs were obtained from the 2007 Medicare fee schedules (Table 2). Primary outcome measures included lifetime risk of cervical cancer, average lifetime cost per patient, and quality-adjusted life expectancy (QALE). The QALE, which combines morbidity and mortality measures, was used to represent the number of healthy years of life for each patient [9]. Disease-specific utilities, which range from 0 (death) to 1 (perfect health), were used to incorporate quality-of-life decrements [21]. Alternative screening strategies were compared using the incremental cost-effectiveness ratio (ICER), which is defined as the additional cost of a specific screening strategy divided by its additional clinical benefit compared to the next most effective strategy.

We conducted extensive sensitivity analyses to assess the impact of all variables on the overall cost-effectiveness results. The range of values used for sensitivity analysis was based on published literature and clinician input as shown in Table 1.

The model was calibrated to match the age-specific prevalence of HPV infection to within ±0.5 percentage points of the data in the literature (Fig. 2). We then matched model predications to the overall prevalence of HPV-type-specific CIN and cervical cancer (data available from authors). To validate the model, we conducted 10 Monte Carlo simulations of 100,000 women each (one million total). In these simulations, the margin of error (standard deviation) was less than 0.02% of total lifetime cost per patient and less than 0.01% of the average life expectancy. The variation in number of cervical cancer deaths between simulations was less than 10 deaths per 100,000 women for the genotyping strategies.

Table 1
Input variables and sources*.

Clinical variable	Base-case value	Range	Source
Population variables			
Annual hysterectomy rate† (%)	0.02–1.17		Keshavarz‡
Age-specific prevalence of HR HPV infection†§(%)	4–31	||	Apple¶
Probability of disease progression			
Prevalence of LSIL among patients with HR HPV infection (%)	14	||	Herrero [12]
RR of LSIL among patients with HPV-16 and HPV-18 infection**	1	||	Assumption
Prevalence of CIN 2,3 among patients with HR HPV infection (%)	4	||	Khan [13]
Rate of progression from CIN 1 to CIN 2,3 among patients with non 16/18 HR HPV infection	0.09	||	Khan [13], Wheeler [2]
RR of progression from CIN 1 to CIN 2,3 in patients with HPV-16 infection**	4.6	||	Khan [13], Wheeler [2]
RR of progression from CIN 1 to CIN 2,3 in patients with HPV-18 infection**	2.5	||	††
Cervical cancer incidence (per 100,000 women)	9.4	||	Saraiya [14]
Prevalence of HPV-16 in patients with cervical cancer (%)	59	55–63	Clifford [15], Munoz [1]
Prevalence of HPV-18 in patients with cervical cancer (%)	13	11–15	Clifford [15], Munoz [1]
Prevalence of non 16/18 HR HPV types in patients with cervical cancer (%)	28	22–34	Clifford [15], Munoz [1]
Probability of disease regression			
Rate of clearance of non 16/18 HR HPV infection	1.29	||	Trottier [16]
RR of clearance of HPV-16 infection**	0.85	||	Trottier [16]
RR of clearance of HPV-18 infection**	0.96	||	Trottier [16]
Regression rate of LSIL among patients with non 16/18 HR HPV infection	0.98	||	Schlecht [17]
RR of regression of LSIL in patients with HPV-16 and HPV-18**	0.91	||	Schlecht [17], Assumption
Regression rate of HSIL among patients with non 16/18 HR HPV infection	0.77	||	Schlecht [17]
RR of regression of HSIL in patients with HPV-16 and HPV-18**	0.27	||	Schlecht [17], Assumption
Screening tests (%)			
Liquid-based cytology (ASCUS or worse)			
CIN 1 or worse			Ratnam [18]
Sensitivity	43		
Specificity	85		
CIN 2,3 or worse			Cuzick [19]
Sensitivity	53		
Specificity	85		
HPV-positive			
CIN 1 or worse			Bigras [20]
Sensitivity	57		
Specificity	96		
CIN 2,3 or worse			Cuzick [19]
Sensitivity	96		
Specificity	91		
Initial efficacy of treatment (%)			
CIN 1	98	95–100	Sanders [21]
CIN 2	95	90–98	Sanders [21]
Invasive cervical cancer‡‡	15–90	10–100	Janicek [22], Pecorelli [23], Perez [24]

* Only variables not previously presented in other publications of this model [11] are included in this table. All variables are annual unless otherwise noted. HR denotes high-risk, HPV human papillomavirus, CIN cervical intraepithelial neoplasia, LSIL low-grade squamous intraepithelial lesion, RR relative risk, FIGO International Federation of Gynecology and Obstetrics, HSIL high-grade squamous intraepithelial lesion, NCDB National Cancer Database, and ASCUS atypical squamous cells of undetermined significance.
† These data vary based on age. The range of values is shown.
‡ Source: Keshavarz H, Hillis SD, Kieke BA, Marchbanks PA. Hysterectomy surveillance — United States, 1994–1999. In CDC surveillance summaries (July 12) MMWR July 12, 2002/51 (SS05); 1–8.
§ These data also vary by HPV type.
|| Unless otherwise indicated, parameters were varied over a range of 0.5 to 2 times the base-case value in sensitivity analyses.
¶ Source: Apple R, Butcher A, Blunk M, Derion T, Eber D, Friedland E, et al. Prevalence of high-risk (HR) HPV genotypes in a US general screening population with normal cytology. 2008. [unpublished data].
** Compared to patients with non 16/18 HR HPV infection.
†† Estimated using a Markov model to match the incidence of CIN 2,3 and cervical cancer in the United States.
‡‡ These data vary based on cervical cancer stage (FIGO I, II, III or IV).

Results

Table 3 shows the lifetime incidence of cervical cancer cases and cervical cancer-related deaths per 100,000 women. Screening for cervical cancer and its precursors prevented 770–940 cervical cancer cases and 640–740 cervical cancer-related deaths per 100,000 women screened. Compared to screening using LBC + HPV triage every two years, HPV genotyping strategies reduced the incidence of cervical cancer by 12–23% and prevented an additional 51–73 deaths per 100,000 women depending upon the genotyping strategy. Compared to co-screening, use of the genotyping strategies prevented additional 4–26 deaths per 100,000 women.

Use of HPV genotyping to triage all high-risk HPV-positive women every three years had an ICER of $34,074 per QALY compared to HPV and LBC co-screening. HPV genotyping with co-screening was the most effective strategy and had an ICER of $33,807 per QALY compared to HPV genotyping for all high-risk HPV-positive women.

Sensitivity analysis

We compared the current clinical practice of co-screening to co-screening + HPV genotyping in one-way sensitivity analysis. The tornado diagram in Fig. 3 shows the range of ICERs for key variables in the model. Model results were sensitive to HPV incidence rate, relative risk of progression of CIN for HPV-16 and -18, and the risk of progression to cervical cancer for all HPV types. Cost of the HPV tests and the cost of colposcopy and biopsy also had a significant impact on the ICERs. Overall, HPV genotyping remained cost-effective. The model results

Table 2
Cost variables.*

Variable	Base-case value	Range
Cost per clinic visit for routine screening	$66	$50–$83
Cost per clinic visit for repeat screening	$97	$73–$121
Diagnostic test costs		
Liquid-based cytology	$28	$21–$35
HPV DNA testing	$49	$37–$61
Linear array HPV genotyping test†	$100	$75–$125
Colposcopy only	$172	$129–$215
Colposcopy with biopsy	$399	$299–$499
Colposcopy with endocervical curettage	$424	$318–$530
Treatment costs		
LLETZ	$1279	$959–$1599
Conization	$1768	$1326–$2210
Cryosurgery	$212	$159–$265
Total abdominal hysterectomy	$35,402	$26,552–$44,253
Vaginal hysterectomy	$35,241	$26,431–$44,051
Radical abdominal hysterectomy	$36,176	$27,132–$45,220
Chemotherapy	$5062	$3797–$6328
Radiotherapy (EBRT)	$10,509	$7882–$13,136
Radiotherapy (EBRT with brachytherapy)	$17,778	$13,334–$22,223
Treatment costs based on stage of disease		
CIN 1 and CIN 2,3	$1086	$815–$1358
FIGO stage I cancer	$53,621	$40,216–$67,026
FIGO stage II cancer	$26,206	$19,655–$32,758
FIGO stage III and stage IV cancer	$26,014	$19,511–$32,518

* All costs are in 2007 USD and are based on 2007 Medicare reimbursement unless otherwise noted. HPV denotes human papillomavirus, LLETZ large loop excision of the transformation zone, EBRT external beam radiation therapy, CIN cervical intraepithelial neoplasia, and FIGO International Federation of Gynecology and Obstetrics.
† The cost of the linear array is an assumption.

were also sensitive to the sensitivity and specificity of LBC and standard HPV tests. If the sensitivity of LBC is more than 10% higher or the sensitivity of the standard HPV test is more than 15% lower than the values we used in the model, the HPV genotyping strategy would no longer be a cost-effective option with an ICER greater than $100,000.

In addition, we modeled the impact of reducing the frequency of screening on the overall cost-effectiveness of the HPV genotyping strategies. Decreasing the frequency of screening improved the cost-effectiveness of HPV genotyping. Screening every 5 years instead of every 3 years saved an additional $1000 per quality-adjusted life-year saved compared to the no screening strategy. However, this resulted in an additional 40–50 cervical cancer-related deaths over a lifetime.

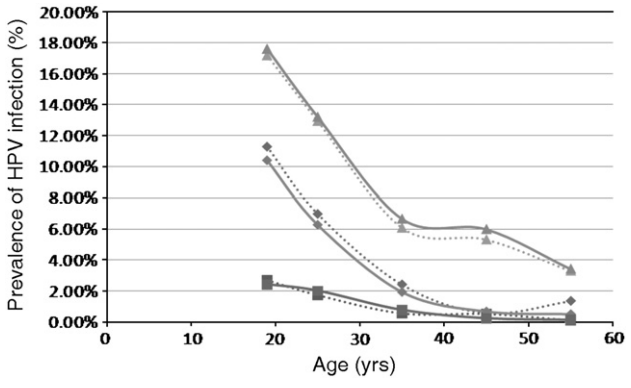

Fig. 2. Prevalence of HPV infection in the United States. The dotted lines denote data from the literature and the solid lines denote data predicted by the model. Lines marked with squares represent HPV-16 infection, lines marked with diamonds represent HPV-18 infection, and lines marked with triangles represent infection with non-16/18 high-risk HPV types. HPV denotes human papillomavirus and yrs denotes years.

Discussion

We found that adding HPV-16 and -18 genotype triage to current cervical cancer screening strategies in the United States resulted in fewer cervical cancer-related deaths, longer quality-adjusted life expectancy, and ICERs that were very cost-effective (i.e., below per capita GDP) [27]. The HPV + LBC triage strategy was highly cost-effective with an ICER of $2618. This finding is consistent with recent results out of India that found that a single round of HPV testing (but not cytologic testing or visual inspection of the cervix with acetic acid) was associated with a significant reduction in cervical cancer cases and deaths from cervical cancer compared to the control group where there was no screening [28].

Based on a Pub Med search (1966-January 2010; English language; search terms: "HPV", "genotyping", and "cost-effectiveness"), we believe that this is the first study to assess the cost-effectiveness of cervical cancer screening algorithms incorporating HPV genotyping. However, numerous studies have demonstrated the cost-effectiveness of incorporating HPV DNA testing into cervical cancer screening programs in the United States [29–31]. These studies have found HPV DNA testing to be cost-effective as either a triage test for equivocal cytology (ASCUS) results or as a primary screening test in conjunction with cytology (co-screening) in women over 30 years of age, as long as screening does not occur more frequently than once every three years.

One of the strengths of the modeling approach that we used was the ability to determine the impact of HPV genotyping on survival and cost-effectiveness over a woman's lifetime, a length of follow-up that is impractical for a clinical trial [32]. Another advantage of our model was that it compared the current use of HPV DNA testing as an adjunct to cytology to the potential use of HPV DNA testing as a primary screening tool as well as HPV DNA testing in conjunction with HPV genotyping.

Our study has several limitations. First, we have modeled two possible HPV genotyping scenarios, including one of the strategies recommended in recently published guidelines [3]. However, there are other potential screening algorithms and other possible applications of HPV genotyping, such as its use as a primary screening test or for post-treatment monitoring for recurrence [33], which were not included in this model. Second, we have not incorporated the impact of HPV vaccination on the screening strategies evaluated in our model. However, given the recent introduction of HPV vaccination in the United States for women aged 11–26 years, the cohort in our model that is eligible for HPV genotype triage (women age 30+) today represents an unvaccinated group in the United States. In addition, our results probably reflect a conservative evaluation of the cost-effectiveness of HPV testing given the likely negative impact that HPV vaccination will have on the performance of cytology relative to that of HPV testing, though this hypothesis will require further research [34–36]. Third, there are limited data available on the risk of progression and regression of HPV and CIN for specific HPV genotypes and for women infected with more than one HPV genotype. However, the prevalence of CIN 2,3 and invasive cervical cancer predicted by the model closely matched the data in the literature. In addition, we tested all assumptions through extensive sensitivity analysis and our results remained consistent over a range of plausible values. Fourth, we have not included data on the performance characteristics of the HPV genotyping test in the model because of the lack of literature on sensitivity/specificity of the genotyping test stratified by high-risk HPV/cytology results and the underlying disease in a screening population. In addition, we were not able to identify any studies that evaluated the sensitivity/specificity of the HPV genotyping test in women who had already received a high-risk HPV test. Given that the known prevalence of HPV-16 and HPV-18 in the U.S. population and in the model is based on the currently available HPV genotyping test, we have assumed that the current genotyping test is the gold standard and is therefore 100% sensitive and specific. We recommend incorporating these data in the model once they become available. Finally, because a standard reimbursement for the HPV

Table 3
Health and economic outcomes — lifetime incidence of disease per 100,000 women, costs, QALE, and ICERs compared to next most effective strategy and to no screening.[a]

Screening strategy[†]	Cervical cancer cases	Cervical cancer deaths	Annual incidence of cervical cancer	Costs ($)	QALE (years)	ICER ($/QALY)	ICER compared to no screening ($/QALY)
No screening	1383	894	20.64	$86,700	28.5866	–	–
LBC (2-year interval)	615	259	9.17	$88,162	28.6623	$19,321	$19,321
LBC + HPV triage (2-year interval)	574	231	8.56	$88,221	28.6651	$21,304	$19,376
HPV + LBC triage (3-year interval)	527	193	7.86	$88,226	28.6670	$2618	$18,980
Co-screening (3-year interval)	502	184	7.49	$88,303	28.6714	$17,204	$18,903
HPV only + HPV genotyping (3-year interval)	507	180	7.57	$88,340	28.6725	$34,074	$19,092
Co-screening + HPV genotyping (3-year interval)	444	158	6.62	$88,407	28.6745	$33,807	$19,420

[a] ICER denotes incremental cost-effectiveness ratio, QALE quality-adjusted life expectancy, QALY quality-adjusted life year, LBC liquid-based cytology, HPV human papillomavirus, and HR high-risk.
[†] Refer to supplementary appendix for detailed screening strategies.

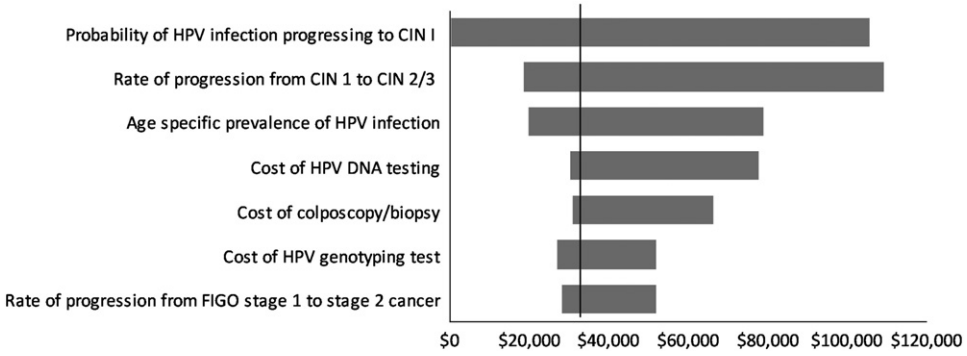

Fig. 3. Tornado diagram: one-way sensitivity analysis showing the range of incremental cost-effectiveness ratios (ICER) comparing co-screening with co-screening + HPV genotyping. The vertical line represents the base-case analysis ICER. HPV denotes human papillomavirus, CIN cervical intraepithelial neoplasia, and FIGO International Federation of Gynecology and Obstetrics.

genotyping test has not yet been established, we assumed a cost of $100 for the test in the model, which is approximately two times the cost of the standard HPV test available today. Although the model results were sensitive to the cost of both the standard HPV test and the HPV genotyping test, we found that the HPV genotyping strategies remained cost-effective throughout the range of test costs we evaluated in sensitivity analyses (standard HPV test: $37 to $61, HPV genotyping test: $75 to $125).

Additional clinical studies are needed to refine our understanding of the effect of different HPV genotypes on the risk of progression and regression of HPV and CIN, as well as to determine the clinical effectiveness of using HPV DNA testing alone and using HPV genotyping in conjunction with HPV DNA testing and/or cytology for primary cervical cancer screening. Our analysis provides evidence of the cost-effectiveness of HPV genotyping based on currently available data. These findings will require confirmation when additional clinical and cost data become available.

In our model, the addition of HPV-16 and -18 genotype triage to current cervical cancer screening strategies in the United States was clinically effective and very cost-effective. Policymakers should consider the use of HPV genotyping triage as one strategy to increase the positive predictive value and cost-effectiveness of current cervical cancer screening algorithms.

Conflict of interest statement
This study was funded by a grant from Roche Molecular Systems, Inc., Pleasanton, CA, United States (Roche). All authors have received honoraria or consultancy fees from Roche. Representatives from Roche were allowed to review model results as well as a draft of the manuscript, but all final decisions regarding model calculations and manuscript content were made by the authors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ygyno.2010.07.004.

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