The Clinical and Economic Benefits of Co-Testing Versus Primary HPV Testing for Cervical Cancer Screening: A Modeling Analysis

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Abstract

Background: Consensus United States cervical cancer screening guidelines recommend use of combination Pap plus human papillomavirus (HPV) testing for women aged 30 to 65 years. An HPV test was approved by the Food and Drug Administration in 2014 for primary cervical cancer screening in women age 25 years and older. Here, we present the results of clinical-economic comparisons of Pap plus HPV mRNA testing including genotyping for HPV 16/18 (co-testing) versus DNA-based primary HPV testing with HPV 16/18 genotyping and reflex cytology (HPV primary) for cervical cancer screening.

Methods: A health state transition (Markov) model with 1-year cycling was developed using epidemiologic, clinical, and economic data from healthcare databases and published literature. A hypothetical cohort of one million women receiving triennial cervical cancer screening was simulated from ages 30 to 70 years. Screening strategies compared HPV primary to co-testing. Outcomes included total and incremental differences in costs, invasive cervical cancer (ICC) cases, ICC deaths, number of colposcopies, and quality-adjusted life years for cost-effectiveness calculations. Comprehensive sensitivity analyses were performed.

Results: In a simulation cohort of one million 30-year-old women modeled up to age 70 years, the model predicted that screening with HPV primary testing instead of co-testing could lead to as many as 2,141 more ICC cases and 2,041 more ICC deaths. In the simulation, co-testing demonstrated a greater number of lifetime quality-adjusted life years (22,334) and yielded $39.0 million in savings compared with HPV primary, thereby conferring greater effectiveness at lower cost.

Conclusions: Model results demonstrate that co-testing has the potential to provide improved clinical and economic outcomes when compared with HPV primary. While actual cost and outcome data are evaluated, these findings are relevant to U.S. healthcare payers and women's health policy advocates seeking cost-effective cervical cancer screening technologies.

Introduction

OVER THE PAST SEVERAL DECADES, cervical cancer screening in the United States has reduced mortality rates of cervical cancer from the leading cause of cancer death in women to ranking 14th. Increased adoption of the Pap test as a screening tool was largely responsible for the decrease through improved detection and treatment of cervical intraepithelial neoplasia (CIN).[1] Yet even with the success of cervical cancer screening, it is estimated that this year in the United States there will be 12,900 new cases of cervical cancer and 4,100 women will die of this disease.[2] Technological advances such as vaccination and testing for human papillomavirus (HPV) have the potential to decrease cervical cancer rates even further.[3–6] Because of its greater sensitivity, combination Pap plus HPV testing is the preferred screening strategy for women 30 to 65 years of age compared with HPV testing or Pap testing alone, while Pap testing is

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recommended for women aged 21 to 30 due to the lower specificity of HPV testing in this population.[7] Controversies regarding appropriate cervical screening intervals and the recent United States Food and Drug Administration approval of an HPV test as a primary cervical cancer screen have raised questions among patients, clinicians, and payers regarding the clinical and cost effectiveness of various cervical cancer screening strategies.[8,9]

Data from several European trials has shown effectiveness for HPV primary screening, with some studies concluding that HPV primary testing can support screening intervals as long as 6 years.[10,11] Additionally, a cost-effectiveness study performed using the results of the ARTISTIC trial determined that HPV testing would be cost effective as a primary screen.[12] However, these studies have generally compared HPV primary screening with Pap testing rather than Pap plus HPV testing and have been performed in populations with single-payer healthcare and differing screening utilization compared with the United States.[13,14] Long-term, large-population studies investigating the cost effectiveness and clinical impact of HPV primary screening are necessary to determine the effectiveness of HPV primary screening in the United States compared with the current clinical practice of Pap plus HPV testing.

At least one attempt has been made to use modeling data to estimate the cost effectiveness of different cervical screening strategies in the United States.[15] However, several factors that may affect the cost effectiveness of HPV primary screening have not been investigated. First, the cost effectiveness of HPV testing in women aged 25 to 29 has not been assessed. Because the Food and Drug Administration approved an HPV primary test for women ≥25 years of age,[9] a model including various screening strategies at different ages would provide practical insights into the cost effectiveness of HPV primary testing in varying age populations where it may be used. Second, while the previous analysis compared Pap plus HPV without genotyping to HPV primary with genotyping, the impact of HPV genotyping on cost effectiveness has not previously been incorporated into economic modeling when comparing Pap plus HPV testing with HPV primary screening.[15] Reflex genotyping for HPV 16/18 following Pap plus HPV testing is recommended by the major guidelines (when the result is a negative Pap and a positive HPV test),[7] so comparing Pap plus HPV screening paradigms that include genotyping with an HPV primary screening paradigm that includes genotyping is necessary for a like comparison. Third, while the previously published model analyzed Pap plus HPV testing using a DNA-based assay, the majority of US diagnostic labs use mRNA-based HPV testing performed with Pap.[16]

Although guidelines currently recommend a 5-year screening interval for Pap plus HPV, this continues to be the subject of ongoing debate in the scientific community as clinical data[5] and modeling analyses from the U.S. Preventative Services Task Force (USPSTF) suggest that screening intervals longer than 3 years may result in substantial increases in cervical cancer morbidity and mortality.[8,17] The USPSTF model developed by Kulasingam et al. found that co-testing intervals of 3 versus 5 years would result in 4.73 versus 7.44 cases of cervical cancer and 0.74 versus 1.35 deaths per 1,000 women, increasing invasive cervical cancer (ICC) cases by 57% and cervical cancer deaths by 82%.[17] Kinney et al.[8] calculated that this increase

predicts that adopting 5-year screening intervals will result in an additional 1 in 369 screening-compliant women contracting ICC and 1 in 1,639 screening-compliant women dying of cervical cancer. Additionally, surveys of practice patterns suggest that the majority of clinicians continue to screen with Pap plus HPV more often than every 5 years,[18–20] versus the 2012 guidelines, which recommended a 5-year interval.[7] Because of these data and published guidance for HPV primary recommending that ''re-screening after a negative primary high-risk HPV screen should occur no sooner than every 3 years,''[21] we believe that a comparison of Pap plus HPV (i.e., ''co-testing'') and HPV primary with equivalent intervals of 3 years is most clinically relevant.

We attempted to address the limitations of previous work with the objective of performing clinical and economic comparisons between cervical cancer screening with Pap plus HPV mRNA testing with genotyping for HPV 16/18 (co-testing) versus primary HPV DNA testing with genotyping for HPV 16/18 and reflex cytology (HPV primary). We present the results of an analysis using a hypothetical cohort of one million 30-year-old women modeled up to age 70 in which co-testing and HPV primary were assessed by comparing the number of cases and deaths from invasive cervical cancer (ICC), expected and predicted quality-adjusted life years (QALYs), and estimated costs associated with each screening strategy. We also present the results of sensitivity analyses investigating the effects of test performance characteristics, mortality rates, and a comparison of HPV primary testing with Pap testing in women 25 to 29 years of age.

Methods

Economic model overview

In this study, we perform clinical-economic comparisons of two cervical cancer screening strategies: Pap plus HPV mRNA testing with genotyping (co-testing) and primary HPV DNA testing with genotyping and reflex cytology (HPV primary). The model estimates the impact within a cohort of one million 30-year-old women receiving high-risk HPV screening. Outcomes and costs were simulated from ages 30 to 70 years. Differences in outcomes between the two scenarios were accumulated annually across each cohort's life span. Outcomes included total and incremental differences in costs, ICC cases, ICC deaths, and QALYs for cost-effectiveness calculations. Data for this study was derived from published literature and analysis of insurance claims records.

Study population

To conduct the evaluation, we constructed a hypothetical cohort of one million women with cervical cancer risk representative of today's population who would be eligible to begin cervical cancer screening at age 30 years per consensus guidelines.[7] The cohort was assumed to experience the same natural history of disease, screening, diagnosis and treatment in a U.S. healthcare setting and followed from age 30 years to age 70 years. A secondary analysis of women aged 25 to 29 years was also performed.

Development of ICC has a long latency period and nearly all cases are associated with persistent high-risk HPV subtypes.[22] Key clinical attributes include high rates of natural

clearance of HPV infection and age-dependent persistence among these strains. Disease progression follows a defined series of stages, from initial HPV infection through progressive stages of cervical lesion development prior to the appearance of cervical cancer.[23]

Screening strategies

We modeled cervical cancer screening strategies using concurrent ThinPrep liquid-based cytology and high-risk HPV mRNA testing (ThinPrep® Pap Test and Aptima® HPV Assay, Hologic, Inc.) with HPV16 18/45 genotyping (co-testing) compared with primary high-risk HPV DNA testing with HPV 16/18 genotyping (cobas® HPV test, Roche Diagnostics US) with reflex for women testing HPV positive but HPV 16/18 negative to ThinPrep liquid-based cytology (HPV primary). Women were assumed to be screened once every 3 years for either screening strategy.[7,8,19] In the model, women testing positive entered a 1-year retesting cycle until a negative screen was observed; colposcopies were performed on women testing positive for (a) HPV 16/18; (b) other high-risk HPV and cytology ≥ "atypical squamous cells of undetermined significance" (ASCUS); (c) cytology ≥ "low grade squamous intraepithelial lesion" irrespective of the HPV results; or (d) other high-risk HPV for two consecutive screening tests. Colposcopies were assumed to be 100% sensitive and specific for CIN2/3. Compliance with periodic screening was held constant at 100% for all testing strategies for the sake of equalizing the analytical comparisons and eliminating bias against tests with lower sensitivity from a factor exogenous to the focus of our analyses. In addition, we chose not to incorporate adherence into the modeling analyses because one-half of the 12,000 women diagnosed with cervical cancer in the United States in 2012 had not been screened within 5 years,[24] and screening compliance varies widely and is dependent upon factors such as age, education, and socioeconomic status.[25] With consideration of this important evidence, we felt that incorporating treatment adherence had the potential for generating misleading results rather than adding to the clinical relevance of our approach.

Model structure

A health state transition (Markov) model with 1-year cycling was developed in TreeAge Pro 2015 (TreeAge Software, Inc.) using epidemiologic, clinical, and economic data from healthcare databases and published literature. Numerous researchers have developed population-level natural history models of the development and progression from initial HPV status through development of ICC.[23,26,27] The conceptual foundation and structure of these models are similar and have served as the basis for health policy and guidelines development over the past 15 to 20 years.[23] Probabilities used to model natural history of viral clearance, disease progression, and regression were taken from a large federally funded epidemiology modeling program housed at the USPSTF,[23] except where noted.

In this health-state transition model, cohort women were assumed to be in one of seven mutually exclusive health states: HPV HR (−), HPV HR (+), CIN1, CIN2, CIN3, ICC, and dead. Within the dead state, patients could either die from ICC or all other causes (Supplementary Fig. S1; Supplementary Data are available online at www.liebertpub.com/jwh). At the end of each annual cycle, women could either remain in the current state, transition to a more severe disease state or death, or transition to a less severe health state. Age-specific transition probabilities of high-risk HPV infection, CIN clearance, progression, and regression are detailed in Table 1.

Model inputs

Test performance was defined as the sensitivity and specificity of the overall screening strategy and is detailed in Table 2. Base case sensitivity and specificity estimates were defined based on previously reported values for detecting CIN3.[28] Because these values were derived from a study that evaluated co-testing utilizing cytology review without automated imaging and HPV testing utilizing a DNA-based assay, the following adjustments were made: co-testing sensitivity was increased from 76.2% to 82.0% to account for the increased sensitivity of cytology with automated imaging;[29] and co-testing specificity was increased from 81.5% to 85.3% to account for the increased specificity of mRNA-based HPV testing.[30–33]

Costs were modeled from the perspective of a U.S. healthcare payer and are reported in 2014 U.S. dollars. Our cost accounting approach was comprehensive and included all costs associated with diagnostic tests and procedures (including colposcopy and biopsy), additional and repeat testing, medical office visits, cancer treatment costs, and end-of-life care. Costs for diagnostic tests and procedures were derived based on the number of diagnostic tests performed and unit cost data from current payment levels using the Truven Health Analytics MarketScan® Research Databases (Truven Health Analytics). For example, the cost for HPV primary screening included the sum of the test cost and the cost of additional reflex testing based on disease prevalence and test performance characteristics. Treatment costs for CIN2 or CIN3 were taken from a recent study on the costs of care for these patients,[34] and treatment of CIN2/3 was assumed to be 100% successful. CIN1 was assumed to not be treated and therefore did not incur added costs if discovered. Costs for treating ICC were split into three components to account for high initial costs of care and lower costs in subsequent years for surviving patients.[35] For terminal ICC patients, an additional cost accounting for end-of-life care was added to either the initial or subsequent year depending on the age of death.[35]

Model outcomes

The primary outcome measure was total direct medical costs per woman screened. Direct costs as defined above (screening, diagnostic follow-up, and treatment), were summed during each year and summed over the course of 40 years from 30 to 70 years of age. Additional outcomes included the cumulative number of ICC cases, ICC-related deaths, number of colposcopies, overall cost of screening and diagnosis, and overall cost of treatment.

We also examined the cost effectiveness of each screening strategy using the cost per QALY. Cost effectiveness is represented as incremental cost-effectiveness ratio (ICER). This ratio represents the efficiency of a screening strategy compared with the next best alternative. We defined an ICER threshold of US$50,000 per QALY as good value for a U.S.

TABLE 1. EPIDEMIOLOGIC AND DISEASE PROGRESSION/REGRESSION MODEL DATA INPUTS

	Age group (years)									Reference(s)
	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–70	
Prevalence										
hrHPV	0.211	0.134	0.99	0.076	0.066	0.066	0.059	0.059	0.044	Huh et al. (2015)[15]
hrHPV 16/18	0.330	0.286	0.279	0.203	0.238	0.199	0.193	0.181	0.189	Huh et al. (2015)[15]
Annual transition probabilities										
Progression										
HPV hr (−) to HPV hr (+)	0.050	0.010	0.010	0.010	0.010	0.005	0.005	0.005	0.005	Kulasingam et al. (2011)[23]
HPV hr (+) to CIN1	0.054	0.054	0.054	0.054	0.054	0.054	0.054	0.054	0.054	Kulasingam et al. (2011)[23]
HPV hr (+) to CIN2 or CIN3	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.006	0.006	Kulasingam et al. (2011)[23]
CIN1 to CIN2 or CIN3	0.020	0.020	0.060	0.060	0.060	0.060	0.060	0.060	0.060	Kulasingam et al. (2011)[23]
CIN2 or CIN 3 to ICC	0.010	0.040	0.040	0.040	0.040	0.040	0.040	0.040	0.040	Kulasingam et al. (2011)[23]
CIN2 to CIN3	0.020	0.020	0.020	0.020	0.020	0.020	0.020	0.020	0.020	Assumption
Regression										
HPV hr (+) to HPV hr (−)	0.500	0.250	0.250	0.150	0.150	0.050	0.050	0.050	0.050	Kulasingam et al. (2011)[23]
CIN1 to HPV hr (+) or HPV hr (−)	0.100	0.100	0.060	0.060	0.060	0.060	0.060	0.060	0.060	Kulasingam et al. (2011)[23]
CIN2 or CIN3 to CIN1	0.030	0.030	0.030	0.030	0.030	0.030	0.030	0.030	0.030	Kulasingam et al. (2011)[23]
CIN2 or CIN3 to HPV hr (−)	0.030	0.030	0.030	0.030	0.030	0.030	0.030	0.030	0.030	Kulasingam et al. (2011)[23]
Mortality										
ICC (co-testing)	0.02085	0.02085	0.02085	0.02085	0.02085	0.02085	0.02085	0.02085	0.02085	Huh et al. (2015)[15]
ICC (HPV primary testing)	0.03250	0.03250	0.03250	0.03250	0.03250	0.03250	0.03250	0.03250	0.03250	Blatt et al. (2015)[6]
All-cause	0.00056	0.00072	0.00103	0.00154	0.00249	0.00374	0.00522	0.00778	0.01243	US Social Security Administration (2010)[44]

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; hr, high risk; ICC, invasive cervical cancer.

TABLE 2. COSTS, SENSITIVITY/SPECIFICITY, AND HEALTH UTILITIES MODEL INPUTS

Variable	Base case	Reference(s)
Annual discount rate		
Costs and QALYs	3.0%	Assumption
Unit costs (2014 USD)*		
Treatment of CIN2 or CIN3	$1,345	Vijayaraghavan et al. (2010)[34]
Colposcopy plus biopsy	$304.78	Huh et al. (2015)
Cytology	$30.23	50/50 blended of image/nonimaged slides; CPT codes 88142, 88175
HPV hr genotyping	$43.58	CPT code 87624
HPV hr pooled test	$43.58	CPT code 87624
Office visit (routine/repeat screening)	$74.55	Huh et al. (2015),[15] CPT code 88305
Treatment of ICC (initial)	$55,684	Mariotto et al. (2011)[35]
Treatment of ICC (continuing)	$1,597	Mariotto et al. (2011)[35]
Treatment of ICC (terminal)	$110,033	Mariotto et al. (2011)[35]
Sensitivity[†]		
Co-testing	0.820	Cox et al. (2013);[28,a] ThinPrep® Imaging System, Hologic (2003)[29,b]
Cytology	0.680	Cox et al. (2013);[28,a] ThinPrep® Imaging System, Hologic (2003)[29,b]
HPV primary	0.720	Cox et al. (2013)[28,a]
Specificity[†]		
Co-testing	0.853	Cox et al. (2013);[28,a] Ting et al. (2015);[30,c] Monsonego et al. (2011);[31,d] Iftner et al. (2015);[13,e] APTIMA® SSED, Hologic (2013)[33,f]
Cytology	0.876	Cox et al. (2013)[28,a]
HPV primary	0.852	Cox et al. (2013)[28,a]
Five-year survival rate[†]		
Co-testing	90%	Howlander et al. (2012)[45]; Blatt et al. (2015)[6,g]
HPV primary	85%	Howlander et al. (2012)[45]; Blatt et al. (2015)[6,g]
Cytology	85%	Howlander et al. (2012)[45]; Blatt et al. (2015)[6,g]
Health utilities		
Well	1.00	Huh et al. (2015)[15]
CIN1	0.97	Huh et al. (2015)[15]
CIN2	0.97	Huh et al. (2015)[15]
CIN3	0.97	Huh et al. (2015)[15]
ICC	0.71	Huh et al. (2015)[15]

*Costs were adjusted to 2014 U.S. dollars (USD) using the medical care component of the Consumer Price Index.
[†]Estimated variable values.
[a]Study included ThinPrep® Pap Test without the ThinPrep® Imaging System, HPV Linear Array® HPV Genotyping Test, Amplicor® HPV Test, and cobas® HPV Test.
[b]Study included ThinPrep® Pap Test slides assessed with either the ThinPrep® Imaging System or manual review.
[c]Study included modeled results for ThinPrep® Pap Test and Aptima® HPV and Hybrid Capture® 2 assays.
[d]Study included ThinPrep® Pap Test and Aptima® HPV and Hybrid Capture® 2 assays.
[e]Study included ThinPrep® Pap Test and Aptima® HPV, Hybrid Capture® 2, and INNO-LiPA® HPV Genotyping Extra assays.
[f]Study included ThinPrep® Pap Test and Aptima® HPV and 16 18/45 GT assays.
[g]Study included ThinPrep Pap Test®, SurePath™ Pap Test, and Hybrid Capture® 2 assay.
CPT, common procedural terminology; QALY, quality-adjusted life-year.

payer, which has been described elsewhere.[36] QALY weights associated with each health state in our model are summarized in Table 2.

Nationwide projection

For policy makers, we also projected the potential economic and clinical impact of each screening strategy on the total U.S. population. For each outcome, total costs, ICC cases, and ICC deaths, we first ran the model for individual cohorts in 5-year increments (e.g., starting at age 30 for 40 years, age 35 for 35 years, age 40 for 30 years, etc.) to reflect the impact that could be expected if a scenario was implemented immediately across a cross-section of the U.S.

population. For each outcome, the model generates the marginal impact for the age group. Total costs or ICC cases and ICC deaths equal the marginal impact estimated in each age-stratified cohort times the female U.S. population in each age category. Net impact was estimated based on the net difference summed across the population.

Sensitivity analyses

We conducted one-way deterministic sensitivity analyses on selected parameters, including test performance characteristics, prevalence rates, mortality rates, and costs. In addition to comparing co-testing to HPV primary in women ≥30 years of age, we also explored the impact of HPV primary

TABLE 3. OUTCOMES, COSTS, AND COST EFFECTIVENESS FOR THE TWO CERVICAL CANCER SCREENING STRATEGIES

Outcome	Ages 30–70 years		
	Co-testing	HPV primary	Net difference[a]
ICC cases per 10,000	57.61	79.02	−21.41
ICC deaths per 10,000	23.06	43.47	−20.41
Lifetime QALYs[b]	23.0084	22.9861	0.0223
Screening costs (USD)	$1,319	$1,129	$189
Treatment costs (USD)	$1,007	$1,236	−$228
Total costs (USD)	$2,326	$2,365	−$39
ICER[c] (USD)			−$1,725 (co-testing dominant)

[a]Net difference = Co-testing − HPV primary.
[b]QALYs reported as per woman screened.
[c]Incremental cost-effectiveness ratio (ICER) = ΔCost / ΔQALY.

versus cytology with ASCUS reflex to high-risk HPV among women aged 25 to 29 years who initiate screening at age 25. Estimated rates of disease progression and regression and test-performance characteristics vary between the USPSTF and other recently published models (Supplementary Table S1).[15,23] We compared the outcomes among this patient population to determine the potential impact of initiating frontline screening with HPV at age 25.

Results

Model results

The results of the model analyses comparing co-testing with HPV primary are shown in Table 3. The patient population for the model analysis is composed of a hypothetical cohort of one million women aged 30 years undergoing alternative cervical screening strategies over 40 years. Lifetime cumulative costs of screening and management per patient equaled $2,326 for co-testing and $2,365 for HPV primary. For co-testing, screening and diagnosis costs equal $1,319 and $1,007 respectively, while for HPV primary, they are $1,129 and $1,236 respectively. The model calculated lower overall total costs associated with co-testing compared with HPV primary, representing an overall savings of $39 over the course of a woman's lifetime.

Co-testing resulted in a slight decrease in lifetime colposcopies per woman compared with HPV primary (2.227 vs. 2.232 respectively), representing 4,557 fewer colposcopies in the one-million-woman cohort. In addition, co-testing resulted in more true positive colposcopies per woman compared with HPV primary (0.127 vs. 0.122 respectively) and fewer false positive colposcopies (2.101 vs. 2.111). These numbers represent 5,206 more true positive colposcopies and 9,763 fewer false positive colposcopies across the entire cohort.

HPV primary testing was calculated to result in as many as 21 additional ICC cases per 10,000 women screened and 20 additional ICC deaths per 10,000 compared with co-testing. The model also calculated a greater number of QALYs per women screened for co-testing at 23.01 compared with HPV primary at 22.99. These results demonstrate a greater effectiveness and lower cost of co-testing that dominates the HPV primary screening strategy.

With the results translated to the one-million-woman cohort, the model predicted that as many as 2,141 ICC cases and 2,041 ICC deaths could be prevented with co-testing vs HPV primary screening. Co-testing demonstrated a greater number of lifetime QALYs (22,334) and yielded $39.0 million in savings compared with HPV primary.

Nationwide projection

The model results were used to calculate a projection to demonstrate the impact at the U.S. national level (Table 4). Using a cross section of the total U.S. female population of 78.9 million women between 30 and 70 years of age,[37] the

TABLE 4. NET COST SAVINGS PROJECTED TO THE NATIONAL LEVEL

Age (years)	Co-testing	HPV primary	Net difference[a]	Female U.S. population	Population distribution	Total costs		Lifetime cost savings[b]
						Co-testing	HPV primary	
30–34	$2,326	$2,365	−$39	9,965,599	13%	$23,179,983,274	$23,568,641,635	−$388,658,361
35–39	$2,298	$2,370	−$72	10,137,620	13%	$23,296,250,760	$24,026,159,400	−$729,908,640
40–44	$2,130	$2,207	−$77	10,496,987	13%	$22,358,582,310	$23,166,850,309	−$808,267,999
45–49	$1,917	$1,991	−$74	11,499,506	15%	$22,044,553,002	$22,895,516,446	−$850,963,444
50–54	$1,688	$1,755	−$67	11,364,851	14%	$19,183,868,488	$19,945,313,505	−$761,445,017
55–59	$1,383	$1,438	−$55	10,141,157	13%	$14,025,220,131	$14,582,983,766	−$557,763,635
60–64	$1,067	$1,102	−$35	8,740,424	11%	$9,326,032,408	$9,631,947,248	−$305,914,840
65–69	$666	$672	−$6	6,582,716	8%	$4,384,088,856	$4,423,585,152	−$39,496,296
Total				78,928,860				−$4,442,418,232

[a]Net difference = Co-testing − HPV primary.
[b]Lifetime cost savings = Total co-testing costs − Total HPV primary costs.

TABLE 5. SENSITIVITY ANALYSIS VALUES

Parameter	Base case value	Lower range	Upper range
Sensitivity of co-testing	82%	76.2%	85%
Specificity of co-testing	85.3%	81.5%	88.7%
Sensitivity of HPV primary	72%	67.8%	76.2%
Specificity of HPV primary	85.2%	81.5%	88.7%
Five-year survival for ICC (HPV primary)*	85%	—	90%
Cost of colposcopy biopsy	$304.78	$274.30	$335.26
Cost of HPV genotyping	$43.58	$39.22	$47.94
Cost of HPV pooled testing	$43.58	$39.22	$47.94
Cost of ICC incremental	$1,597	$1,437.30	$1,756.70
Cost of ICC initial	$55,684	$50,115.60	$61,252.40
Cost of ICC terminal	$110,033	$99,029.70	$121,036.30
Cost of office visit	$74.55	$67.10	$82.01
Cost of CIN2 & CIN3	$1,345	$1,210.50	$1,479.50

*The base case value of 5-year ICC survival is 90% for co-testing and 85% for HPV primary; the sensitivity analysis tested the impact of varying 5-year ICC survival for HPV primary to 90%.

model predicts approximately 150,000 additional ICC cases and more than 100,000 additional ICC deaths using an HPV primary approach compared with co-testing. This represents an overall additional lifetime cost of approximately $4.4 billion for HPV primary.

One-way sensitivity analysis

A one-way sensitivity analysis was performed on the model to test the influence of several key parameters. The primary factors tested were test performance for co-testing and HPV primary screening, costs of the tests and treatments, and 5-year survival for invasive cervical cancer. The ranges of values used for each of the factors in the sensitivity analysis can be found in Table 5.

Tornado diagrams were created for each of the four major outcomes of interest: cumulative total costs; QALYs; ICC cases per 10,000; and ICC deaths per 10,000 women. All four analyses show that both clinical and cost outcomes are highly sensitive to the performance of the screening tests. Figure 1A shows the results of the one-way sensitivity analysis for the net difference of the cumulative total costs. The difference in cumulative total costs between co-testing and HPV Primary screening ranged from −$179 per woman (i.e., cost savings conferred by co-testing) to $111 per woman (i.e., additional cost conferred by co-testing). Total costs were most sensitive to the specificity of co-testing, followed by specificity of HPV primary, sensitivity of HPV primary, and then sensitivity of co-testing. When the specificity of co-testing approached the high value of 88.7%, co-testing saved $166 per woman when compared with the base case savings of $39. When the specificity of co-testing was set to 81.5%, the specificity of DNA-based co-testing reported by Cox et al.,[28] co-testing resulted in an incremental cost of $111 per woman. In the other three analyses, the most influential parameter was the sensitivity of HPV primary followed by the sensitivity of co-testing.

Figure 1B–D shows the results of the one-way sensitivity analysis varying the test performance characteristics of co-testing and HPV primary for the clinical outcomes of QALYs, ICC cases, and ICC deaths. In the simulation, sensitivity analysis demonstrated that co-testing provided clinically superior outcomes (greater QALYs, fewer ICC cases, fewer

ICC deaths) compared with HPV primary across the entire range of inputs.

Sensitivity analysis for women 25–29 years old

A second sensitivity analysis was performed to determine the impact of transition probabilities cited in Huh et al.[15] and Kulasingam et al.[23] on women aged 25 to 29 years. Huh et al. generally cites a higher rate of progression to the various health states as well as a higher rate of regression when compared with the USPSTF data used by Kulasingam et al. (Supplementary Table S1).[15,23]

Overall, both sets of transition probabilities demonstrate that cytology with ASCUS reflex has greater cost savings in our model; however, cytology has a slightly higher number of ICC cases but not ICC mortality when compared with HPV primary (Supplementary Table S2). Use of USPSTF data progression tables resulted in a greater number of net ICC cases per 10,000 compared with using the Huh progression tables (0.51 vs. 0.26). Both progression tables found a similar number of net ICC deaths per 10,000 (0.03 vs. 0.02). Using the Huh data, HPV primary generated an ICER of $611,818 compared with an ICER of $426,667 with USPSTF data, indicating that HPV primary is not cost effective compared with cytology in women screened between the ages of 25 and 29 years using either USPSTF or Huh data as inputs (Supplementary Table S2).

Sensitivity analysis for ICC mortality calibrated to Surveillance, Epidemiology, and End Results Program data

A third sensitivity analysis was performed to test the impact of calibrating ICC mortality rates (Table 1), which were held constant in the model for all simulation years in the base-case analysis, against multiyear survival curves derived from Surveillance, Epidemiology, and End Results (SEER) Program cervical cancer data to reflect the tapering effect observed in AJCC stage 1 survival after 5 years following diagnosis.[38] To replicate this effect in the model data, all ICC mortality rates were reduced by 50% after the fifth year of simulation post diagnosis (i.e., the ICC mortality rates in Table 1 were halved for women with ICC diagnosis who survived to year 6 and beyond). The impact of making this change on modeling
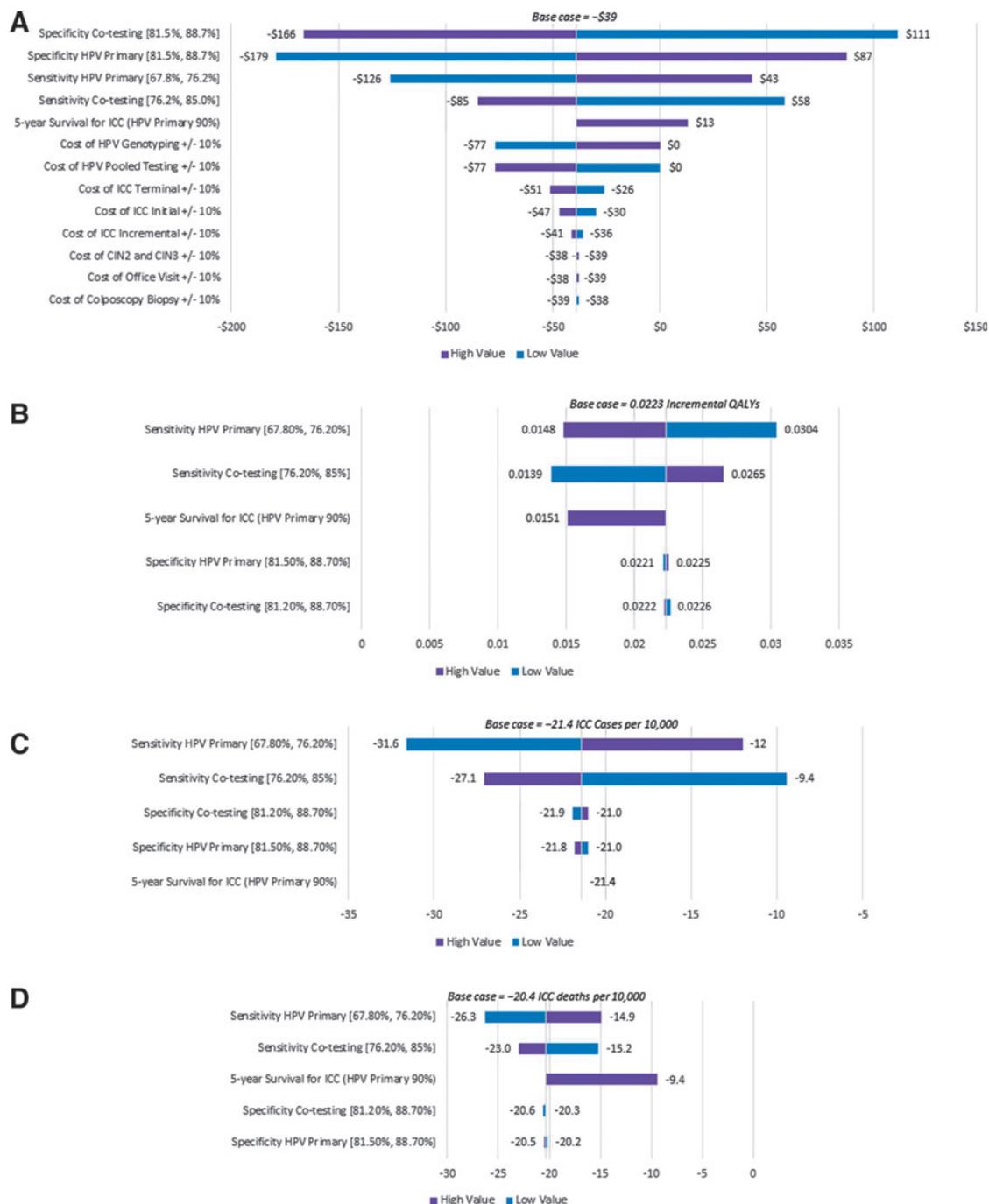
FIG. 1. One-way sensitivity analyses. **(A)** Sensitivity analysis of model parameter variation on net cost savings. **(B)** Sensitivity analysis of model parameter variation on incremental QALYs. **(C)** Sensitivity analysis of model parameter variation on number of ICC cases per 10,000 women. **(D)** Sensitivity analysis of model parameter variation on number of ICC deaths per 10,000 women.

analysis results was small (Supplementary Table S3). As expected, the number of ICC cases remained unchanged relative to the base-case analysis, but the number of ICC deaths decreased by about 33% and 30% for co-testing and HPV primary respectively. The impact on QALYs was negligible and the impact on costs was small, with the net difference in total costs only decreasing from $39 in cost savings per woman to $15 in cost savings per woman over the 40-year simulation time horizon. In terms of cost effectiveness, co-testing con-

ferred greater benefit (more QALYs) at less cost compared with HPV primary and therefore remained the economically dominant screening strategy.

Although useful for benchmarking purposes, as described here, notable limitations of the SEER mortality data include the fact that the data are 15–28 years old and geographically limited (collected in 1988 to 2001 from 12 SEER geographic areas covering only about 14% of the total U.S. population), the data pertain specifically to women diagnosed with

squamous carcinoma of the cervix uteri, and the data were derived from the pool of women who may or may not have been screened by co-testing, HPV primary, or another screening method prior to their diagnosis.

Discussion

As discussions about appropriate cervical cancer screening strategies examine net outcomes by balancing benefits and harms, clinical-economic comparisons are useful to guide decision making. This model demonstrates that among women 30 to 70 years of age, cervical cancer screening using co-testing at 3-year intervals may be more cost effective and prevent more cases of cervical cancer compared with primary HPV screening at 3-year intervals. Co-testing dominated the HPV primary screening strategy, with lower lifetime screening and management costs and greater effectiveness as determined by ICC cases and deaths without increasing harms as measured by lifetime colposcopies/woman.

The model predicted an additional 2,141 ICC cases and 2,041 ICC deaths over 40 years with HPV primary compared with co-testing among the hypothetical one-million-woman cohort. These results are due to the greater sensitivity of co-testing compared with HPV primary. The small difference between ICC cases and deaths is the result of an increased likelihood of detecting cancer at a later, less treatable stage using HPV primary. Projected nationally, these results predict a substantial decrease in human and monetary costs over a lifetime of screening. Additionally, slightly higher QALYs per woman were calculated for co-testing. Sensitivity analyses determined that test sensitivity for both HPV primary and co-testing had a greater impact than specificity or ICC survival rate in determining QALYs or ICC mortality. These results suggest that test sensitivity is vital to consider when attempting to improve outcomes of cervical screening programs.

Calculations for cost effectiveness generated similar results for HPV primary testing and co-testing, with an approximate savings of $39 per woman, over 40 years, using co-testing. Improvements in total costs were most sensitive to variations in test specificity followed by test sensitivity. With cost differences approaching neutral (i.e., $39 cost savings in the base case, and a tight range of −$179 to $111 per screened woman in the sensitivity analyses), comparisons should focus on the improved clinical outcomes and net health benefits of co-testing. In the model, co-testing provided superior clinical outcomes (greater QALYs, fewer ICC cases, fewer ICC deaths) compared with HPV primary across a range of test performance characteristics.

Regarding strategies for women between 25 and 29 years of age, a sensitivity analysis evaluating cost effectiveness of cytology with ASCUS reflex and HPV primary determined that HPV primary was not cost effective compared with cytology with ASCUS reflex in this age group. A DNA HPV test was approved for use as a primary screen in women ≥25 years of age,[9] even though HPV testing of women under 30 years of age is controversial due to the additional harms and lack of established additional clinical benefit associated with HPV testing.[7,39] These data provide further evidence that while HPV primary testing in women 25 to 29 years of age is likely to identify more cases of CIN2/3, very few of these CIN2/3 cases will progress to ICC before the age of 30. Thus, the model shows that HPV primary testing in this age group offers minimal benefit in cancer detection, does not decrease mortality from cervical cancer, and is not cost effective compared with cytological testing. Additionally, HPV primary testing in this age group resulted in a higher number of colposcopies. While the harms of excess colposcopies were not modeled here, recommendations that women younger than 30 years of age not be tested for HPV are the result of data suggesting that the harms associated with overtreatment are a significant consideration in this population.[7]

This analysis has several advantages over prior clinical-economic models that have evaluated HPV primary screening as an alternative cervical screening strategy for women in the United States. An analysis published by Huh et al. in 2015 using data from the ATHENA trial compared cost effectiveness of HPV primary testing with genotyping and cytology triage to HPV primary testing with cytology triage only and co-testing without genotyping in a hypothetical cohort of women, leading to a conclusion that use of an HPV test with genotyping improves cost effectiveness.[15,40] However, direct comparison between HPV primary testing vs co-testing using HPV tests with genotyping for both strategies was not assessed until this study. A cost-effectiveness study conducted using data from a UK study found that HPV primary screening may be cost effective compared with cytology alone, but the study was performed in a population with a national health system, with markedly differing cervical screening compliance compared with the United States.[12] A cost-effectiveness analysis using a Dutch model found that HPV screening was cost effective compared with cytology alone, but the authors cautioned that HPV primary screening is affected by being "well controlled" and evenly distributed throughout the population.[41] Thus, caution should be used when extrapolating from European to U.S. cost-effectiveness studies.

There are several limitations to this model. As mentioned above, unscreened and underscreened women were not considered. This is relevant, as approximately half of all cervical cancer cases in the United States occur in this population.[42] Assumptions of 100% sensitivity and specificity for colposcopy and 100% success for CIN2/3 treatment also limit the application of model results to real-world conditions, as does our failure to account for the impact of increasing rates of HPV vaccination.[43] HPV vaccination rates will affect the cervical cancer rate as well as the cost effectiveness of cervical cancer screening strategies. Finally, this analysis is limited by the lack of long-term data regarding HPV primary screening. Large-scale longitudinal studies are needed to determine the effectiveness of HPV primary screening strategies in U.S. women.

In summary, mRNA-based co-testing with HPV 16/18 genotyping dominated the DNA-based HPV primary screening with HPV 16/18 genotyping, with lower lifetime screening and management costs combined with fewer colposcopies as well as lower ICC incidence and mortality. Although it identifies more cases of CIN2/3, the addition of HPV testing to cytology in women 25 to 29 years of age provides minimal benefit in cancer detection, does not decrease mortality from cervical cancer, and is not cost effective compared with cytological testing.

Conclusion

More than 50 years after the introduction of the Pap test, cervical cancer remains a significant public health burden,

underscoring the need for a clinically effective screening approach. The recent introduction of an HPV test for primary screening has re-opened the discussion regarding the optimal cervical screening paradigm. The results of this model demonstrate that co-testing has the potential to provide improved clinical and economic outcomes when compared with HPV primary. While actual cost and outcome data are evaluated, these findings are relevant to U.S. healthcare payers and women's health policy advocates seeking cost-effective cervical cancer screening technologies.

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