The Budget Impact of Cervical Cancer Screening Using HPV Primary Screening

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ABSTRACT

Objectives: This study assessed the clinical and budgetary impacts of human papillomavirus (HPV) primary screening with HPV16/18 genotyping, in contrast to current cervical cancer screening strategies.

Study Design: A decision-tree framework and Markov model were used to model clinical and cost implications of screening and diagnosis of disease.

Methods: A model was developed to compare the annual clinical and budgetary impact of HPV screening with genotyping versus cytology, and co-testing with and without genotyping. Epidemiology and test performance inputs are from the literature and the Addressing THE Need for Advanced HPV Diagnostics (ATHENA) trial. Costs are from a US payer perspective. Clinical impact was measured as the resulting incidence of cervical cancer, and budget impact is reported as annual cost per screened woman. The model considered the impact of patient noncompliance (loss to follow-up) at both the initial screen and re-test.

Results: Cytology was found to be inferior to both co-testing and HPV primary screening. Co-testing was inferior to co-testing with genotyping. Co-testing with genotyping every 3 years (incidence = 5.5 per 100,000 women; annual investment = $61) or 5 years (incidence = 7.4 per 100,000 women; annual investment = $37) was slightly more effective, but more costly than HPV primary screening every 3 years (incidence = 6.2 per 100,000 women; annual investment = $48) or 5 years (incidence = 8.1 per 100,000 women; annual investment = $30). Genotyping strategies were relatively stable to the effects of patient noncompliance.

Conclusions: Primary HPV screening with genotyping represents a sensible combination of clinical effectiveness and costs, while reducing the risks associated with patient noncompliance.

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In 2014, a human papillomavirus (HPV) test that detects high-risk types and individual genotypes HPV 16 and 18 utilizing amplification of target DNA (the cobas HPV Test) was approved by the FDA for primary screening in cervical cancer. HPV types 16 and 18 have been found to cause more than 70% of cervical cancers[1]; women who are positive for HPV 16 and/or 18 are at an increased risk of high-grade cervical intraepithelial neoplasia (CIN), even if they have normal cytology.[2,3] CIN is a dysplastic change beginning at the squamocolumnar junction in the uterine cervix that may be a precursor of cervical cancer: grade 1 (CIN1), mild dysplasia involving the lower one-third or less of the epithelial thickness; grade 2 (CIN2), moderate dysplasia with one-third to two-thirds involvement; grade 3 (CIN3), severe dysplasia or carcinoma in situ, with two-thirds to full-thickness involvement. Targeting detection of these high-risk HPV types allows clinicians to properly manage patients at highest risk for developing cervical cancer.

In 2015, a panel represented by multiple societies issued new interim guidance recommending HPV primary screening as an alternative to current cytology-based screening strategies.[4] This provides clinicians and patients with another option for routine screening—options which now include cytology alone, cytology in conjunction with HPV testing (co-testing) with or without genotyping, or HPV primary screening with genotyping.[5,6] Likewise, payers now have the opportunity to consider an expanded range of screening options.

This study was undertaken to estimate, from a US payer perspective, the near-term clinical and budgetary impacts of adopting HPV primary screening with HPV 16/18 genotyping compared with current cervical cancer screening strategies derived from established clinical guidelines.

METHODS

A decision-tree framework was used to model the screening and diagnosis of disease ≥CIN2; a Markov transition

Take-Away Points

Human papillomavirus (HPV) screening with genotyping represents a sensible combination of clinical effectiveness and costs.

- Recent FDA approval and an interim clinical guidance have resulted in HPV testing as an option for primary screening of cervical cancer.
- HPV screening with genotyping every 3 years leads to a lower incidence of cervical cancer than either of the 2 current guideline-recommended strategies—cytology every 3 years or co-testing every 5 years—with 6.2 of cervical cancer cases per 100,000 women versus 11.7 and 7.4, respectively. There is also lower cost per disease detected ($32,123 vs $36,876 and $36,196, respectively).
- Incorporating genotyping into screening is especially important as the screening interval increases or when patient compliance is a concern.

model was constructed to simulate the natural history of HPV, CIN, and cervical cancer. Women enter the decision tree with the probability of initial disease representative of a US cervical cancer-screened population of individuals 30 years or older (mean age = 45 years).

The model compares the screening strategies currently recommended by the United States Preventive Services Task Force (USPSTF)/American Cancer Society (ACS) for women aged 30 to 65 years with strategies that incorporate HPV screening with genotyping to identify high-risk strains 16 and 18, resulting in comparison of 7 screening strategies in total. The screening strategies include: 1) cytology every 3 years, 2) co-testing every 3 years, 3) co-testing every 5 years, 4) co-testing with genotyping every 3 years, 5) co-testing with genotyping every 5 years, 6) HPV primary screening with genotyping every 3 years, and 7) HPV primary screening with genotyping every 5 years.[5,6] The decision-tree diagrams are represented in Figure 1. A diagnosis of ≥CIN2 incurs treatment cost and exits the model.

Screening Algorithms

The screening algorithms are described as follows:

Cytology every 3 years. Cytology is the primary screening method. Women with indeterminate cytology results—referred to as atypical squamous cells of undetermined significance (ASC-US)—are triaged using HPV testing. A positive HPV result or cytology worse than ASC-US leads to colposcopy. Women with negative results return for routine cervical cancer screening in 3 years (see Figure 1A).

Co-testing every 3 or 5 years. The USPSTF/ACS recommend a second screening strategy of co-testing with cytology and HPV, which allows extension of the screening interval from 3 to 5 years for women negative on both tests. Colposcopy is indicated in women with cytology results of ASC-US/HPV positive, or cytology worse than ASC-US, regardless of HPV result. Women with normal cytology but who are HPV positive return for follow-up co-testing in 12 months. Although 5-year screening intervals are recommended for women negative on both tests, in practice, a 3-year interval is frequently used. Both intervals were modeled (see Figure 1B).

Co-testing with genotyping every 3 or 5 years. Another option for women with co-testing results of normal cytology but who are HPV positive is to genotype for HPV 16/18. Women testing positive for 16/18 are sent to colposcopy, whereas women positive for HPV but negative for 16/18 repeat co-testing in 12 months. All other co-testing results are managed the same way as for co-testing without genotyping (see Figure 1B).

HPV primary screening every 3 or 5 years. This strategy utilizes HPV with genotyping as the primary screening modality. Women who are HPV negative return for routine screening in 3 or 5 years. Women who are HPV 16/18 positive are referred for immediate colposcopy. HPV positive women who are HPV 16/18 negative have cytology performed on the residual sample. A cytology result of ASC-US or worse leads to immediate colposcopy, whereas normal results from cytology return women for follow-up testing in 12 months (see Figure 1C).

Model Structure

Consistent with published US rates, the model assumes a 75% probability of compliance with follow-up testing and routine screening intervals.[7,8] Similarly, patients lost to follow-up at the time of re-test are assumed to have a 75% probability of returning to routine screening at the next interval. In the interim, patients with HPV infection/CIN may persist, progress, or regress from one stage to another.

The progression and regression of HPV and CIN were modeled using a Markov state transition model with a 1-month cycle, which captures the probability of a screened population of individuals 30 years or older, transitioning to a more or less advanced stage of CIN or HPV infection. Women enter the Markov model following results of the initial screen in 1 of the following 8 health states: well and HPV negative, non-16/18 HPV positive, 16/18 HPV positive, CIN1, CIN2, CIN3, invasive cervical cancer (ICC), or death.

Figure 2 shows the graphical representation of the Markov model. We assume only CIN3 may directly progress to ICC. Patients face a probability of death from ICC; however, death from other causes is not considered.

The model was used to assess the impact of the screening strategies over 2 screening cycles (2x interval length). The results of the model were then annualized to arrive

Figure 1. Model Diagrams

Figure 1A. Cytology

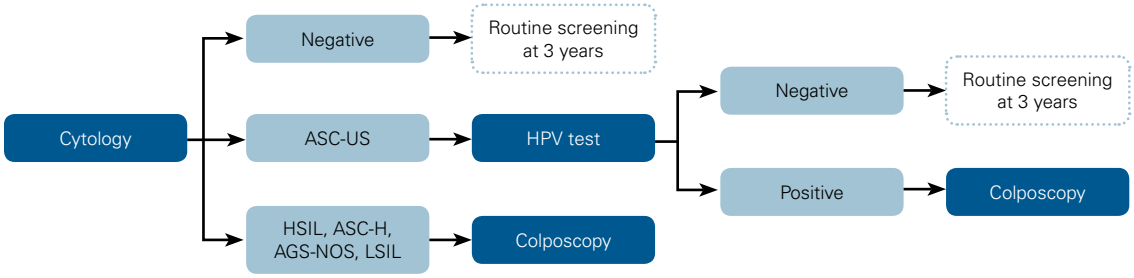


Figure 1B. Co-testing (with and without genotyping)

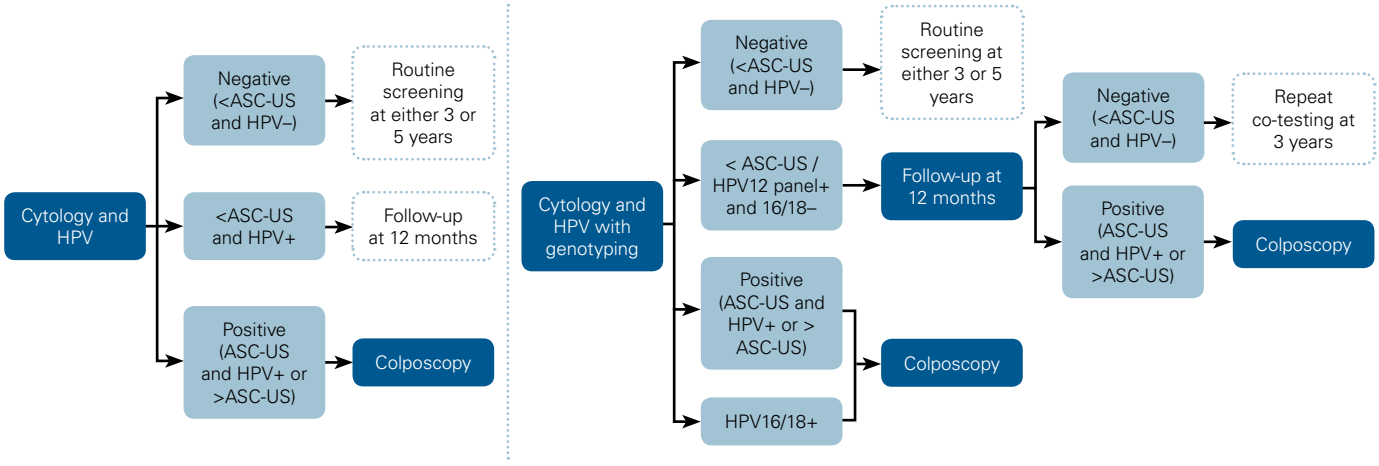
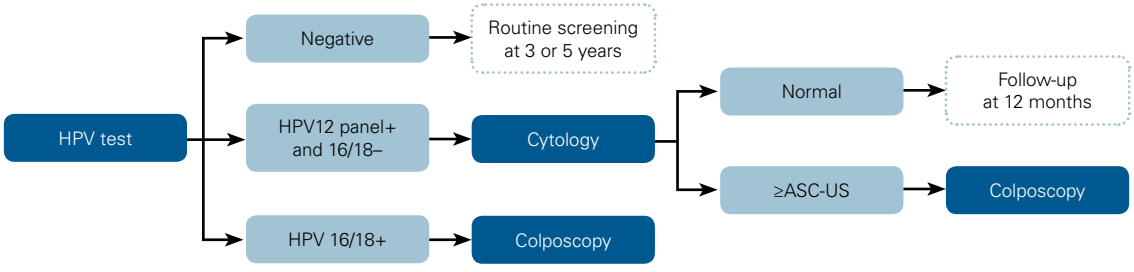


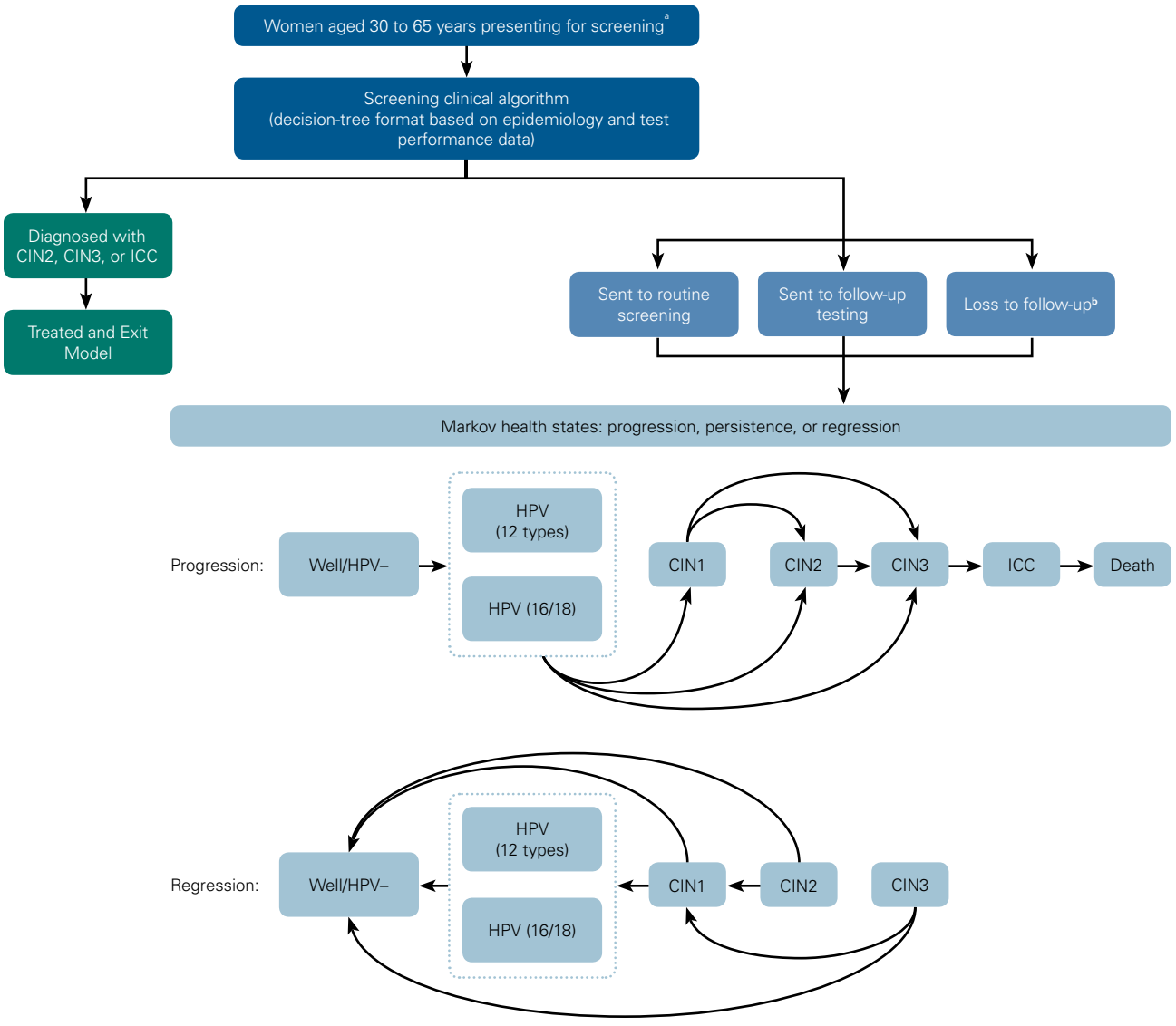
Figure 1C. HPV primary screening



AGS-NOS indicates atypical glandular cells not otherwise specified; ASC-H, atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; indicates CIN, cervical intraepithelial neoplasia with CIN1, 2, and 3 indicating higher severity of dysplasia; HSIL, high-grade squamous intraepithelial lesion; HPV, high-risk human papillomavirus; HPV16/18 refers to 2 high-risk types, HPV16 and HPV18; ICC, invasive cervical cancer.

at a 1-year time horizon that reports the expected annual incidence of cervical cancer and average annual cost of screening women 30 years or older (see **eAppendix** [eAppendices available at **www.ajmc.com**] for calculation). Annual outcomes were reported in order to normalize results across screening strategies with different interval lengths and to present the data on a basis that is easier for payers to compare. The model uses probabilities instead of a cohort approach to allow each payer to assess the impact on their population by multiplying the annual per-screened-woman outcomes by their relevant member population. The costs are reported annually and are assumed to be applicable in the short term (6-10 years) as the basis of the calculation is 2 screening cycles. The results assume that

Figure 2. Patient Flow and the Natural History of Cervical Disease



CIN indicates cervical intraepithelial neoplasia with CIN1, 2, and 3 indicating higher severity of dysplasia; HPV, high-risk human papillomavirus; HPV16/18 refers to 2 high-risk types, HPV16 and HPV18; ICC, invasive cervical cancer.
[a]Excludes women with hysterectomies and HIV (~11.4% of population). Assumes a screening participation rate of 77.9%.
[b]Loss to follow-up at re-test and routine screening is assumed to be 25%.

as long as the national population of screened women 30 and older are representative of a health plan's population, the entry/exit of individual members should not impact the overall results, allowing the results to be representative of individual health plans.

Inputs

Epidemiological and test performance inputs were taken from the Addressing THE Need for Advanced HPV Diagnostics (ATHENA) trial and are based on women 30 years or older (mean age = 44.7 ± 10.1 years). The ATHENA trial has been described elsewhere.[9-11] Briefly, as a prospective cohort study which enrolled 47,000 women undergoing cervical cancer screening in the United States, it is the largest cervical cancer screening registrational trial to evaluate HPV testing.

Data used for the natural history of cervical cancer were taken from US and international studies. Clinical inputs are shown in Table 1.[9-32] Where multiple sources existed, inputs were based on a weighted average, with re-

Table 1. Clinical Inputs[9-32]

Input	Base Case[a]	Range	Source
Test Performance			
Cytology (threshold = ASC-US)			
Sensitivity of cytology for CIN2	53.2%	48.1%-58.3%	Cox et al (2013)[9]
Sensitivity of cytology for ≥CIN3	57.7%	50.9%-64.4%	Cox et al (2013)[9]
Specificity of cytology	73.4%	72.0%-74.5%	Cox et al (2013)[9]
Cytology (threshold = LSIL)			
Sensitivity of cytology for CIN2	39.2%	Increase/decrease relative to ASC-US threshold	Castle et al (2011)[10]
Sensitivity of cytology for ≥CIN3	40.1%		Castle et al (2011)[10]
Specificity of cytology	86.5%		Castle et al (2011)[10]
% of population testing ASC-US	3.9%	3.1%-4.6%	Wright et al (2012)[11]
% of population testing LSIL	1.5%	1.2%-1.8%	Wright et al (2012)[11]
% of population testing HSIL	0.3%	0.2%-0.3%	Wright et al (2012)[11]
HPV testing			
Sensitivity of HPV for CIN2	86.4%	83.1%-89.0%	Cox et al (2013)[9]
Sensitivity of HPV for ≥CIN3	89.9%	86.0%-92.4%	Cox et al (2013)[9]
Specificity of HPV	62.7%	61.4%-63.9%	Cox et al (2013)[9]
Genotyping 16/18			
Sensitivity of genotyping 16&18 for CIN2	43.6%	39.4%-47.8%	Cox et al (2013)[9]
Sensitivity of genotyping 16&18 for CIN3	53.4%	47.9%-58.7%	Cox et al (2013)[9]
Sensitivity of genotyping 16&18 for ICC	59.2%	53.1%-65.0%	Cox et al (2013),[9] Guan et al (2012)[12]
Specificity of genotyping 16&18	89.6%	91.3%-87.7%	Cox et al (2013)[9]
Colposcopy			
Sensitivity of colposcopy	100.0%	96%-100%	Mitchell et al (1998),[13] assumption
Specificity of colposcopy	100.0%	48%-100%	Mitchell et al (1998),[13] assumption
Epidemiology[b]			
Prevalence of HPV (all)	8.4%	4.2%-16.8%	Wright et al (2012)[11]
Prevalence of HPV16 and/or HPV18	2.1%	1.1%-4.2%	Wright et al (2012)[11]
Prevalence of CIN1	1.2%	0.6%-2.3%	Wright et al (2012)[11]
Prevalence of CIN2	0.3%	0.1%-0.5%	Wright et al (2012)[11]
Prevalence of CIN3	0.5%	0.2%-1.0%	Wright et al (2012)[11]
Prevalence of ICC	0.053%	0.026%-0.105%	Wright et al (2012)[11]
Annual progression from:			
Well to HPV	4.2%	2.1%-8.5%	Kulasingam et al (2013)[14]
HPV (non 16/18)			
to CIN1	8.1%	6.4%-9.7%	Kulasingam et al (2013),[14] Kjær et al (2010)[15]
to CIN2	0.1%	0.0%-0.6%	Khan et al (2005)[16]
to CIN3	0.1%	0.0%-1.5%	Khan et al (2005)[16]
HPV (16/18 types)			
to CIN1	9.9%	4.3%-15.5%	Kjær et al (2010),[15] Khan et al (2005),[16] Insinga et al (2007),[17] Insinga et al (2011)[18]
to CIN2	0.6%	0.3%-9.9%	Kjær et al (2010),[15] Khan et al (2005),[16] Insinga et al (2007),[17] Insinga et al (2011)[18]
to CIN3	1.5%	0.7%-3.7%	Kjær et al (2010),[15] Khan et al (2005),[16] Insinga et al (2007),[17] Insinga et al (2011)[18]

(continued)

Table 1. Clinical Inputs[9-32] *(continued)*

Input	Base Case[a]	Range	Source
CIN1			
to CIN2	3.2%	2.5%-3.9%	Kataja et al (1989),[19] Holowaty et al (1999),[20] Matsumoto et al (2006)[21]
to CIN3	0.9%	0.7%-1.0%	Kataja et al (1989),[19] Holowaty et al (1999)[20]
to ICC	–	0.0%-0.4%	Kataja et al (1989),[19] Holowaty et al (1999)[20]
CIN2			
to CIN3	4.2%	3.9%-4.5%	Kataja et al (1989),[19] Holowaty et al (1999),[20] Matsumoto et al (2006),[21] Guedes et al (2010),[22] Omori et al (2007)[23]
to ICC	–	0.0%-1.9%	Kataja et al (1989),[19] Holowaty et al (1999),[20] Matsumoto et al (2006),[21] Guedes et al (2010),[22] Omori et al (2007)[23]
CIN3 to ICC	4.5%	0.5%-5.7%	Kulasingam et al (2013),[14] Kataja et al (1989),[19] Holowaty et al (1999),[20] McCredie et al (2008),[24] Sasieni et al (2009),[25] Goldie et al (2004),[26] Mandelblatt et al (2002),[27] Insinga et al (2009)[28]
Annual mortality rate for undetected cervical cancer[c]	11.3%	9%-13.1%	Lorin et al (2015)[29]
Annual regression from:			
HPV (non 16/18)			
to well (with normal smear)	58.6%	42.5%-73.5%	Bulkmans et al (2007)[30]
to well (with ASC-US smear)	45.6%	36.3%-67.3%	Bulkmans et al (2007)[30]
HPV (16/18)			
to well (with normal smear)	43.8%	33.5%-55.4%	Insinga et al (2011),[18] Bulkmans et al (2007)[30]
to well (with ASC-US smear)	21.8%	20.7%-40.7%	Insinga et al (2011),[18] Bulkmans et al (2007)[30]
CIN1			
to well	21.2%	8.6%-29.0%	Kataja et al (1989),[19] Holowaty et al (1999),[20] Matsumoto et al (2006)[21]
to HPV	2.4%	1.0%-3.2%	Kataja et al (1989),[19] Holowaty et al (1999),[20] Matsumoto et al (2006)[21]
CIN2			
to well	9.4%	5.3%-22.1%	Kataja et al (1989),[19] Holowaty et al (1999),[20] Guedes et al (2010),[22] Omori et al (2007)[23]
to CIN1	9.4%	5.3%-22.1%	Kataja et al (1989),[19] Holowaty et al (1999),[20] Guedes et al (2010),[22] Omori et al (2007),[23] Meyskens et al (1994),[31] Castle et al (2009)[32]
CIN3			
to well	3.9%	2.8%-4.6%	Kataja et al (1989),[19] McCredie et al (2008)[24]
to CIN1	1.6%	1.2%-1.9%	Kataja et al (1989),[19] McCredie et al (2008)[24]

ASC-US indicates atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia with CIN1, 2, and 3 indicating higher severity of dysplasia; HPV, human papillomavirus; HPV16/18 refers to 2 high-risk types, HPV16 and HPV18; ICC, invasive cervical cancer; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.
[a]Base case refers to the input itself. The range still assumes the same population but speaks to the uncertainty of the inputs used. The base case are the inputs used for the results reported while the range is used in the sensitivity analysis.
[b]Calculation of epidemiology inputs are available in **eAppendix Table 1**.
[c]The mortality rate is the risk of mortality for women who have cervical cancer missed during screening due to either test performance or loss to follow-up. It is based on the annualized 5-year survival rate.
[d]No category for regression from CIN3 to CIN2 as the literature historically grouped CIN2 and CIN3 together.

sults from studies with larger populations weighted more heavily than studies with smaller populations.

Costs include all screening costs in addition to costs for the diagnosis and treatment of CIN and ICC. Costs for screening, diagnosis, and treatment of CIN are taken from the US Medicare fee schedule.[33] Cost for HPV testing was based on the cobas HPV Test, which includes simultaneous testing for strains 16/18, and therefore, no additional cost was assumed for genotyping. Direct costs for treating ICC were taken from published US studies and assume the average cost of treatment and follow-up across all stages of cervical cancer.[34,35] (Cost inputs are available in **eAppendix 2** [Table]). All costs were adjusted to 2014 US dollars.

A 1-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were undertaken to assess the impact of parameter uncertainty on modeled results. Clinical inputs were varied across the ranges reported in the literature and assumed a beta distribution, while costs were varied by ±50% and assumed a gamma distribution. The correlation between sensitivity and specificity was controlled using the diagnostic odds ratio.[36] The ranges used are shown in Table 1.[9-32] The PSA followed a standard Monte Carlo approach based on 5000 randomly generated simulations of parameter values.

RESULTS

When assessing the costs and effectiveness of each strategy relative to alternatives, screening with cytology alone results in an increase in the incidence of cancer and higher mortality due to missed cancers than any other strategy, and at a cost higher than that of strategies incorporating a 5-year interval. We can thus consider cytology to be inferior to alternatives with 5-year screening intervals since it is both less effective and more expensive.

Of the remaining strategies, co-testing every 3 or 5 years without genotyping has similar costs as co-testing every 3 or 5 years with genotyping, but results in more cancer. Consequently, we can consider the co-testing with genotyping strategies to be superior to co-testing without genotyping. Thus, the strategies that utilize genotyping represent a desired combination of improving screening effectiveness while reducing cost. For instance, HPV primary screening at 5 years, when compared with the current guideline-recommended strategies of: 1) primary cytology every 3 years; and 2) co-testing without genotyping every 5 years, leads to reduced cervical cancer incidence and 27% and 19% reductions in cost, respectively.

Of all strategies modeled, the one that incorporates co-testing with genotyping and HPV primary screening at 3-year intervals results in the lowest annual incidence of cervical cancer (5.5 and 6.2 per 100,000 women, respectively). However, such strategies may require an increase in overall financial investment.

The number needed to screen to avert 1 case of ICC was calculated as the inverse of the absolute risk reduction from modeled screening strategies compared with the current US incidence of cervical cancer for screened women 30 years or older (8.0 per 100,000).[37] As compared with today's environment of mixed methodologies for cervical cancer screening, co-testing with genotyping and HPV primary screening at 3-year intervals result in the lowest numbers needed to screen to detect 1 cancer at 40,000 and 55,556, respectively. Results are shown in **Table 2**.

To assess the impact of loss to follow-up on the performance of the screening algorithms, we compared the linear relationships between compliance and disease incidence for all strategies. The comparison indicates that co-testing every 5 years is most sensitive to noncompliance (slope coefficient = 0.467, where a steeper slope indicates higher sensitivity to noncompliance), followed by co-testing every 3 years (slope coefficient = 0.400). Genotyping strategies are relatively stable to the effect of noncompliance (slope coefficients range between 0.227 for co-testing with genotyping every 3 years to 0.300 for HPV primary screening every 5 years). This suggests that strategies incorporating genotyping may mitigate the effect of noncompliance through early detection of the highest-risk patients at the initial visit.

Full results of the 1-way sensitivity and PSA are available in **eAppendix 4** and **5**, respectively. The 1-way sensitivity analysis, comparing HPV primary screening at 3 years with the alternative strategies, reveals that the costs of HPV screening and cytology as well as the prevalence of HPV had the largest impact on the incremental cost per patient. When comparing a 3- versus 5-year time horizon, the same parameters were impactful; the additional cost of office visits had the largest impact on the cost difference.

PSA results are summarized in **Table 3**. The analysis revealed that HPV primary screening at 3 years is likely to reduce the annual incidence of ICC compared with the other guideline-endorsed strategies of cytology every 3 years and co-testing with or without genotyping every 5 years (100%, 98%, and 75% probability that HPV primary screening will reduce the incidence of ICC versus comparator, respectively), but may increase costs at shortened intervals. The results of the PSA suggest considerable uncertainty regarding effectiveness; this is due to the small population of true positives, which impacts the precision of sensitivity in screening studies.

Table 2. Model Outcomes for Women Aged 30-65 Years in Order of Decreasing Cancer Incidence and Mortality From Missed Cancers

Model Outcome	Annual Cervical Cancer Incidence per 100,000	Incremental Cases Prevented	NNS (incremental to next-lowest rate)	NNS (relative to current screening practices in the United States for screened women aged 30-65 years[a])	Annual Cervical Cancer Mortality Resulting From Missed Cancers per 100,000
Cytology (3 years)	11.7	–	–	–27,027	4.7
Co-testing (5 years)	9.0	2.7	37,037	–100,000	3.2
HPV primary screening (5 years)	8.1	0.9	111,111	–1,000,000	2.8
Co-testing with genotyping (5 years)	7.4	0.7	70,000	166,667	2.5
Co-testing (3 years)	7.4	0	–	166,667	2.3
HPV primary screening (3 years)	6.2	1.2	83,333	55,556	1.8
Co-testing with genotyping (3 years)	5.5	0.7	142,857	40,000	1.4

(continued)

DISCUSSION

When evaluating new strategies for screening, it is critical to consider the clinical benefits that can be achieved with a screening change versus the incremental costs of that change. HPV primary screening every 3 years has the second lowest incidence of cancer and related mortality, yet at a substantially lower cost per screened woman compared with the most effective strategy, co-testing with genotyping every 3 years ($48 vs $61). This represents an opportunity to improve clinical outcomes while balancing resource allocation.

This analysis finds that co-testing with and without genotyping every 3 years leads to the lowest and third lowest incidence of cervical cancer and related mortality, respectively, among all strategies compared. However, these strategies result in the highest cost per screened woman. This implies that while co-testing is highly sensitive to detecting cervical disease, the costs associated with it must be carefully considered.

These results point to the clinical benefit of incorporating genotyping into any screening strategy, with the HPV primary screening scenarios leading to the best balance of disease detection and cost control.

The current analysis provides US payers with information to address the likely shift in cervical cancer screening strategies. Internationally, there is a growing body of evidence that supports practice changes towards HPV screening as a primary screening method. A Swedish trial randomized 12,527 women aged 32 to 38 years attending regular screening into either primary cytology or HPV screening, and found that HPV primary screening detected more women with ≥CIN 2 than cytology did.[38] Furthermore, the Health Council of the Netherlands recommends the use of HPV testing to replace cytology as the primary screening method, based on models concluding that a new HPV testing program may be expected to prevent more cancer cases and deaths than the existing program design, without increasing cost.[39] Finally, the Australian health technology assessment concluded that using HPV with genotyping as the primary cervical screening method is less costly and more effective in reducing cancer incidence and mortality than cytology.[40] Implementations of HPV primary screening in these countries are expected to follow.

The results of our analysis also highlight the need for payers to consider the potential for noncompliance with screening and follow-up, which are important drivers of a successful screening program. In a study examining patients in comprehensive health plans, failure to follow-up contributed to 13% of ICCs.[41] A recent retrospective data analysis from Kaiser Permanente of Northern California found that a negative HPV test result alone was a better predictor of absence of cancer at 3 years than both cytology at 3 years and co-testing results at 5 years.[42] Our study demonstrates that when the compliance rate decreases, strategies that include HPV 16/18 genotyping are less sensitive to its effect. This suggests an opportunity to improve screening, particularly in settings where health-seeking behavior may be less than optimal, such as in the lower socioeconomic sector and in the Medicaid population. Medicaid insures nearly a quarter of women diagnosed with cervical cancer, and approximately half of cervical

Table 2. Model Outcomes for Women Aged 30-65 Years in Order of Decreasing Cancer Incidence and Mortality From Missed Cancers *(continued)*

Model Outcome	Incremental Deaths Prevented	Annual Cost per Screened Patient	Screening Costs	Diagnostic Costs	Treatment Costs	Cost per Disease (≥CIN2) Detected
Cytology (3 years)	–	$41	$33	$3	$5	$36,876
Co-testing (5 years)	1.5	$37	$29	$3	$5	$37,394
HPV primary screening (5 years)	0.4	$30	$22	$3	$5	$30,313
Co-testing with genotyping (5 years)	0.3	$37	$28	$4	$5	$36,196
Co-testing (3 years)	0.2	$60	$48	$5	$7	$39,633
HPV primary screening (3 years)	0.7	$48	$37	$5	$7	$32,123
Co-testing with genotyping (3 years)	0.4	$61	$47	$6	$7	$38,707

CIN indicates cervical intraepithelial neoplasia with CIN1, 2, and 3 indicating higher severity of dysplasia; HPV, human papillomavirus; HPV16/18 refers to two high-risk types, HPV16 and HPV18; ICC, invasive cervical cancer; NNS, numbers needed to screen (to prevent 1 case of ICC).
[a]Formula = 1 ÷ (probability of cervical cancer in United States for screened women aged 30-65 years [8.0 per 100,000 women] – probability of cervical cancer projected in the model for select strategy). The amount 8.0 per 100,000 was used as the current incidence per screened woman aged 30-65 years in the United States, or the baseline for comparison.
See **eAppendix 3** for the calculation of US incidence. Positive results may be interpreted as the numbers needed to screen to avoid 1 cancer relative to the current practice; the negative results represent the numbers needed to screen to miss 1 cancer, and indicate that the strategy is less effective than current US screening.

cancer patients with Medicaid, were diagnosed at late stage despite continuous enrollment.[43,44] Currently, most states offer cervical screening only with cytology for Medicaid patients. The additional benefit of early detection of high-oncogenic-risk HPV genotypes provides critical data to payers on appropriate management, since patients may not be available for follow-up testing or may not seek another screening test within the recommended time frame.

Limitations

As with any predictive modeling study, this analysis is subject to several limitations. Models based on clinical trials can have inherent limitations associated with the design of the trial and the inclusion criteria for patients. The ATHENA trial was a diagnostic cohort study in which the end point was clinically relevant ≥CIN2 cases, rather than ICC, which was a relatively rare event in countries with screening programs. Thus, the prevalence of ICC observed in ATHENA was slightly lower than SEER-reported rates, and may have underestimated the cancer treatment costs and mortality in the model. Nevertheless, ATHENA enrolled women presenting for routine screening across half of the United States at clinics that routinely perform screening and colposcopy. Accordingly, the trial patients could be considered representative of the real-world practice.

Additionally, the impact of HPV 16/18 on progression and regression of CIN is not well understood. In this analysis, transition probabilities for CIN were not stratified by HPV type, which likely underestimates the clinical impact of genotyping. As our understanding of these strains evolves, future analysis should consider their impact on CIN.

This analysis does not consider the impact of HPV 16/18 vaccination on cervical cancer screening. It is expected that the introduction of the HPV vaccine in 2006 will lead to an eventual reduction in the incidence of cervical lesions, further reducing the clinical utility of cytology, which subjectively interprets cellular abnormalities.[45,46] HPV testing that is indicated to detect all 14 high-risk strains provides important coverage, going beyond the specific strains targeted by vaccination. An economic analysis demonstrated that regardless of vaccination status, HPV primary screening for women 30 years or older is expected to be more cost-effective than current screening strategies.[47]

Lastly, this analysis assumed the use of the cobas HPV Test, a test in which genotyping is included as part of the initial HPV test and therefore is not an additional cost in the screening process. While clinical outcomes are expected to be similar with any HPV testing platform, cost impact will differ when considering a test that includes a secondary cost for the genotyping step. Hence, the results of this analysis are not applicable to all HPV genotyping scenarios.

Table 3. Incremental Results and PSA Outcomes for Strategies Compared With HPV Primary Screening (3 years)

Model Outcome Base case, mean, and 95% CI	Incremental annual ICC incidence per 100,000 screened women	Incremental NNS to avoid 1 cancer	Probability that HPV primary screening every 3 years is more effective (ie, decreases ICC) than comparator	Incremental annual cost per screened woman (mean, 95% CI)	Probability that HPV primary screening at 3 years is less costly than comparator
Cytology (3 years)	Base case = –5.5 Mean = –5.2 95% CI, –10.8 to –1.9	Base case = 182 Mean = 235 95% CI, 93-520	100%	Base case = $7 Mean = $7.00 95% CI, –16.51 to 35.20	27%
Co-testing (5 years)	Base case = –2.8 Mean = –1.9 95% CI, –5.5 to 0.0	Base case = 357 Mean = 709 95% CI, 86-3935	98%	Base case = $12 Mean = $11.76 95% CI, –3.81 to –31.15	7%
Co-testing (3 years)	Base case = –1.2 Mean = –0.8 95% CI, –2.2 to 0.2	Base case = 833 Mean = 1607 95% CI, –7261 to 10,771	94%	Base case = –$12 Mean = –$11.91 95% CI, –30.72 to –2.66	100%
Co-testing with genotyping (5 years)	Base case = –1.2 Mean = –0.81 95% CI, –3.93 to 0.54	Base case = 833 Mean = –17 95% CI, –17,241 to 17,650	75%	Base case = $11 Mean = $11.54 95% CI, 4.36-30.83	8%
Co-testing with genotyping (3 years)	Base case = 0.7 Mean = 0.7 95% CI, 0.23-1.54	Base case = –1429 Mean = –1805 95% CI, –4210 to –650	0%	Base case = –$12 Mean = –$12.09 95% CI, –30.10 to –2.82	100%

HPV indicates human papillomavirus; ICC, invasive cervical cancer; NNS, numbers needed to screen; PSA, probabilistic sensitivity analysis.
[a]Formula = 1 ÷ (probability of cervical cancer for comparator – probability of cervical cancer projected in the model for HPV primary screening every 3 years).

CONCLUSIONS

With the recent FDA approval and changes in clinical guidance for HPV primary screening of cervical cancer, payers should expect to see changes in clinical practice for cervical cancer screening. This analysis finds that incorporation of genotyping into cervical screening improves the detection of CIN and thus decreases the incidence of cervical cancer. This is especially important as the screening interval increases or patient compliance is a concern, since genotyping identifies women at highest risk for cervical cancer. Although payers will be expected to provide access to the full suite of guideline-recommended screening strategies, this analysis indicates that HPV primary screening represents a sensible combination of clinical effectiveness and cost.

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REFERENCES

1. de Sanjose S, Quint WG, Alemany L, et al; Retrospective International Survey and HPV Time Trends Study Group. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. *Lancet Oncol.* 2010;11(11):1048-1056. doi:10.1016/S1470-2045

2. Kjær SK, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. *J Natl Cancer Inst.* 2010;102(19):1478-1488. doi:10.1093/jnci/djq356.

3. Berkhof J, Bulkmans NW, Bleeker MC, et al. Human papillomavirus type-specific 18-month risk of high-grade cervical intraepithelial neoplasia in women with a normal or borderline/mildly dyskaryotic smear. *Cancer Epidemiol Biomarkers Prev.* 2006;15(7):1268-1273.

4. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. *Gynecol Oncol.* 2015;136(2):178-182. doi:10.1016/j.ygyno.2014.12.022.

5. Saslow D, Solomon D, Lawson HW, et al; ACS-ASCCP-ASCP Cervical Cancer Guideline Committee. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA Cancer J Clin.* 2012;62(3):147-172. doi:10.3322/caac.21139

6. Cervical cancer: screening. US Preventive Services Task Force website. http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm. Published March 2012. Accessed July 28, 2014.

7. Yabroff KR, Washington KS, Leader A, Neilson E, Mandelblatt J. Is the promise of cancer-screening programs being compromised? quality of follow-up care after abnormal screening results. *Med Care Res Rev*. 2003;60(3):294-331.

8. Insinga RP, Glass AG, Rush BB. Diagnoses and outcomes in cervical cancer screening: a population-based study. *Am J Obstet Gynecol*. 2004;191(1):105-113.

9. Cox JT, Castle PE, Behrens CM, Sharma A, Wright TC Jr, Cuzick J; ATHENA HPV Study Group. Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study. *Am J Obstet Gynecol*. 2013;208(3):184.e1-184.e11. doi:10.1016/j.ajog.2012.11.020.

10. Castle PE, Stoler MH, Wright TC Jr, Sharma A, Wright TL, Behrens CM. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. *Lancet Oncol*. 2011;12(9):880-890. doi:10.1016/S1470-2045(11)70188-7

11. Wright TC Jr, Stoler MH, Behrens CM, Apple R, Derion T, Wright TL. The ATHENA human papillomavirus study: design, methods, and baseline results. *Am J Obstet Gynecol*. 2012;206(1):46.e1-46.e11. doi:10.1016/j.ajog.2011.07.024.

12. Guan P, Howell-Jones R, Li N, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. *Int J Cancer*. 2012;131(10):2349-2359. doi:10.1002/ijc.27485.

13. Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol*. 1998;91(4):626-631.

14. Kulasingam SL, Havrilesky LJ, Ghebre R, Myers ER. Screening for cervical cancer: a modeling study for the US Preventive Services Task Force. *J Low Genit Tract Dis*. 2013;17(2):193-202. doi:10.1097/LGT.0b013e3182616241.

15. Kjær SK, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. *J Natl Cancer Inst*. 2010;102(19):1478-1488. doi:10.1093/jnci/djq356.

16. Khan MJ, Castle PE, Lorincz AT, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. *J Natl Cancer Inst*. 2005;97(14):1072-1079.

17. Insinga RP, Dasbach EJ, Elbasha EH, Liaw KL, Barr E. Progression and regression of incident cervical HPV 6, 11, 16 and 18 infections in young women. *Infect Agent Cancer*. 2007;2:15. doi:10.1186/1750-9378-2-15

18. Insinga RP, Perez G, Wheeler CM, et al; FUTURE I Investigators. Incident cervical HPV infections in young women: transition probabilities for CIN and infection clearance. *Cancer Epidemiol Biomarkers Prev*. 2011;20(2):287-296. doi:10.1158/1055-9965.EPI-10-0791.

19. Kataja V, Syrjänen K, Mäntyjärvi R, et al. Prospective follow-up of cervical HPV infections: life table analysis of histopathological, cytological and colposcopic data. *Eur J Epidemiol*. 1989;5(1):1-7.

20. Holowaty P, Miller AB, Rohan T, To T. Natural history of dysplasia of the uterine cervix. *J Natl Cancer Inst*. 1999;91(3):252-258.

21. Matsumoto K, Yasugi T, Oki A, et al. IgG antibodies to HPV16, 52, 58 and 6 L1-capsids and spontaneous regression of cervical intraepithelial neoplasia. *Cancer Lett*. 2006;231(2):309-313.

22. Guedes AC, Zeferino LC, Syrjänen KJ, Brenna SM. Short-term outcome of cervical intraepithelial neoplasia grade 2: considerations for management strategies and reproducibility of diagnosis. *Anticancer Res*. 2010;30(6):2319-2323.

23. Omori M, Hashi A, Nakazawa K, et al. Estimation of prognoses for cervical intraepithelial neoplasia 2 by p16INK4a immunoexpression and high-risk HPV in situ hybridization signal types. *Am J Clin Pathol*. 2007;128(2):208-217.

24. McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol*. 2008;9(5):425-434. doi:10.1016/S1470-2045(08)70103-7.

25. Sasieni P, Castanon A, Parkin DM. How many cervical cancers are prevented by treatment of screen-detected disease in young women? *Int J Cancer*. 2009;124(2):461-464. doi:10.1002/ijc.23922.

26. Goldie SJ, Kim JJ, Wright TC. Cost-effectiveness of human papillomavirus DNA testing for cervical cancer screening in women aged 30 years or more. *Obstet Gynecol*. 2004;103(4):619-631.

27. Mandelblatt JS, Lawrence WF, Womack SM, et al. Benefits and costs of using HPV testing to screen for cervical cancer. *JAMA*. 2002;287(18):2372-2381.

28. Insinga RP, Dasbach EJ, Elbasha EH. Epidemiologic natural history and clinical management of Human Papillomavirus (HPV) Disease: a critical and systematic review of the literature in the development of an HPV dynamic transmission model. *BMC Infect Dis*. 2009;9:119. doi:10.1186/1471-2334-9-119.

29. Lorin L, Bertaut A, Hudry D, et al. About invasive cervical cancer: a French population based study between 1998 and 2010. *Eur J Obstet Gynecol Reprod Biol*. 2015;191:1-6. doi:10.1016/j.ejogrb.2015.04.007.

30. Bulkmans NW, Berkhof J, Bulk S, et al; POBASCAM Study Group. High-risk HPV type-specific clearance rates in cervical screening. *Brit J Cancer*. 2007;96(9):1419-1424. doi:10.1038/sj.bjc.6603653

31. Meyskens FL Jr, Surwit E, Moon TE, et al. Enhancement of regression of cervical intraepithelial neoplasia II (moderate dysplasia) with topically applied all-trans-retinoic acid: a randomized trial. *J Natl Cancer Inst*. 1994;86(7):539-543.

32. Castle PE, Schiffman M, Wheeler CM, Solomon D. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. *Obstet Gynecol*. 2009;113(1):18-25. doi:10.1097/AOG.0b013e31818f5008.

33. Medicare and Medicaid fee schedule 2014. CMS website. http://www.cms.gov/apps/ama/license.asp?file=/ClinicalLabFeeSched/downloads/14CLAB.zip. Published November 27, 2013. Accessed December 1, 2014.

34. Vijayaraghavan A, Efrusy MB, Goodman KA, Santas CC, Huh WK. Cost-effectiveness of using human papillomavirus 16/18 genotype triage in cervical cancer screening. *Gynecol Oncol*. 2010;119(2):237-242. doi:10.1016/j.ygyno.2010.07.004.

35. Chesson HW, Blandford JM, Gift TL, Tao G, Irwin KL. The estimated direct medical cost of sexually transmitted diseases among American youth, 2000. *Perspect Sex Reprod Health*. 2004;36(1):11-19.

36. Genders TS, Meijboom WB, Meijs MF, et al. CT coronary angiography in patients suspected of having coronary artery disease: decision making from various perspectives in the face of uncertainty. *Radiology*. 2009;253(3):734-744. doi:10.1148/radiol.2533090507.

37. NIH fact sheet: cervical cancer. National Institutes of Health website. http://report.nih.gov/nihfactsheets/viewfactsheet.aspx?csid=76. Updated March 29, 2013. Accessed December 1, 2014.

38. Naucler P, Ryd W, Törnberg S, et al. Human papillomavirus and Papanicolaou tests to screen for cervical cancer. *N Engl J Med*. 2007;357(16):1589-1597.

39. Population screening for cervical cancer. The Health Council of the Netherlands website. http://www.gezondheidsraad.nl/en/publications/preventie/population-screening-for-cervical-cancer. Published May 24, 2011. Accessed December 1, 2014.

40. MSAC outcomes: application no. 1276–renewal of the National Cervical Cancer Screening Program. Australian Government Medical Services Advisory Committee website. http://www.msac.gov.au/internet/msac/publishing.nsf/Content/FD36D6990FFAA639CA25799200058940/$File/1276%20-%20Final%20MSAC%20PSD%20-%20NCSP%20Renewal.pdf. Published April 2014. Accessed July 28, 2014.

41. Leyden WA, Manos MM, Geiger AM, et al. Cervical cancer in women with comprehensive health care access: attributable factors in the screening process. *J Natl Cancer Inst*. 2005;97(9):675-683.

42. Gage JC, Kim JJ. A negative HPV test may predict lower cervical cancer risk than a negative Pap. *J Natl Cancer Inst*. 2014;106(8):dju251. doi:10.1093/jnci/dju251.

43. Bradley CJ, Given CW, Roberts C. Health care disparities and cervical cancer. *Am J Public Health*. 2004;94(12):2098-2103.

44. O'Malley CD, Shema SJ, Clarke LS, Clarke CA, Perkins CI. Medicaid status and stage at diagnosis of cervical cancer. *Am J Public Health*. 2006;96(12):2179-2185.

45. Garland SM. The Australian experience with the human papillomavirus vaccine. *Clin Ther*. 2014;36(1):17-23. doi:10.1016/j.clinthera.2013.12.005.

46. Franco EL, Mahmud SM, Tota J, Ferenczy A, Coutlée F. The expected impact of HPV vaccination on the accuracy of cervical cancer screening: the need for a paradigm change. *Arch Med Res*. 2009;40(6):478-485. doi:10.1016/j.arcmed.2009.06.003.

47. Goldhaber-Feibert JD, Stout NK, Salomon JA, Kuntz KM, Goldie SJ. Cost-effectiveness of cervical cancer screening with human papillomavirus DNA testing and HPV-16, 18 vaccination. *J Natl Cancer Inst*. 2008;100(5):308-320. doi:10.1093/jnci/djn019. ■

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eAppendix 1. Worked Example of Weighted Average Prevalence

Below is a worked example of how the assumed age structure converts to a weighted average prevalence/incidence. The ATHENA trial was the source for all prevalence and incidence data within the model. ATHENA enrolled 47,208 women 21 years or older undergoing routine cervical cancer screening, of which 34,254 women 30 years or older underwent screening with cytology and HPV testing with genotyping of 16 and 18 (Cox et al. *Am J Obstet Gynecol*. 2013;208(3):184.e1-184.e11) between May 2008 and August 2009 at 61 clinical centers across the United States. The population was representative of the US screened population.

Where data for women 30 years or older was not specifically reported, we totaled the incidence across women 30 years or older and divided by the total number of women 30 years or older within the study.

Below are the tables and calculations for hrHPV, HPV16, HPV18, CIN1, CIN2, CIN3 and ICC within the model.

	hrHPV	**HPV16**	**HPV18**
30-34	810	166	64
35-39	634	120	56
40-44	458	65	28
45-49	386	50	28
50-54	300	38	24
55-59	181	22	13
60-64	98	13	5
65-69	32	6	0
>70	28	4	2
Total	**2927**	**484**	**220**
≥30 = (Total/34,254)	**8.4%**[a]	**1.4%**	**0.6%**

[a]hrHPV for women aged over 30 years was reported in Cox et al. *Am J Obstet Gynecol*. 2013;208(3):184.e1-184.e11

Source: Wright et al. Table 3. *Am J Obstet Gynecol*. 2012;206:46.e1-11.

	30-39	**40-49**	**50+**	**Total ≥30**	**Model input ≥30**
CIN1	201	114	82	397	**1.2%**
CIN2	51	29	11	91	**0.3%**
CIN3	104	46	21	171	**0.5%**
ICC	10	6	2	18	**0.053%**
Total	2557	1958	1404	**34,254**	

Source: Wright et al. Table 4. *Am J Obstet Gynecol*. 2012;206:46.e1-11.

eAppendix 2. Worked Example of Annualized Intervals

Worked example of how screening intervals are annualized using incidence of cervical cancer for co-testing at 5 years and HPV at 3 years.

	Scenario	**Co-Testing**	**HPV Primary**
A	**Interval**	**5 years**	**3 years**
B	Calculated progression to ICC 1st interval:	23,233	10,139
C	Calculated progression to ICC 2nd interval:	22,235	8573
D=B+C	Total progression to ICC over 2 intervals	45,468	18,712
E=D/(A*2)	Annual incidence of ICC	45,468/(5×2) **= 4547**	18,712/(3×2) **= 3119**
E / screened pop × 100,000	**Incidence per 100,000** (based on screened population of 50.5M)	4547/50.5M*100,000 **= 9.0**	3119/50.5M*100,000 **= 6.2**

Table. Cost Inputs

Inputs	**Base Case**	**Range**	**Source**
Routine screening office visit	$72.81	$36-$88	CPT 99213 [32]
Liquid-based cytology	$36.41	$18-$44	CPT 88175 [32]
Additional cytology for abnormal smear results	$31.64	$16-$38	CPT 88141[32]
HPV DNA testing	$48.24	$24-$72	CPT 87621 [32]
Diagnostic office visit	$72.81	$36-$88	CPT 99213 [32]
Colposcopy with biopsy	$286.14	$143-$343	CPT 57455, 88305 [32]
Treatment for CIN2/3	$1,292.00	$646-$1,550	[33]
Treatment for invasive cervical cancer	$47,847.00	$23,924-$57,416	[33],[34]

eAppendix 3. Calculation of US Screened Population Incidence for Women Aged 30-65 Years

US annual incidence of cervical cancer	12,900	[1]
Incidence attributed to age 30-65 years	63%	[1],[2]
% cervical cancers attributed to screened population	50%	[3-6]
[A] Total incidence of cervical cancer attributed to screened women 30-65 years	**4,064**	
US total population	313,914,040	[7]
% women aged 30-65 years	23.3%	[7]
% of women with hysterectomies or HIV (HIV patients are screened more intensely than the general population)	11.5%	[8]
Total population of eligible women	64,823,425	calc
Attendance rate for cervical cancer screening	77.9%	[9]
[B] Total population of screened women aged 30-65 years	**50,497,448**	calc

Incidence per 100,000 screened women aged 30-65 years ([A]/[B]x 100,000)	**8.0**	calc

[1] SEER data. Howlader N, Noone AM, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER website, April 2015. Accessed 6/18/15. <http://seer.cancer.gov/statfacts/html/cervix.html>

[2] Benard VB, Watson M, Castle PE, Saraiya M. Cervical carcinoma rates among young females in the United States.External Web Site Icon Obstetrics and Gynecology 2012;120(5):1117–1123. Accessed 6/18/15. http://www.cdc.gov/cancer/dcpc/research/articles/cervical-young-women.htm

[3] Sung HY, Kearney KA, Miller M, Kinney W, Sawaya GF, Hiatt RA. Papanicolaou smear history and diagnosis of invasive cervical carcinoma among members of a large prepaid health plan. Cancer. 2000; 88:2283-9.

[4] Kinney W, Sung HY, Kearney KA, Miller M, Sawaya G, Hiatt RA. Missed opportunities for cervical cancer screening of HMO members developing invasive cervical cancer (ICC). Gynecol Oncol. 1998; 71:428-30.

[5] Leyden WA, Manos MM, Geiger AM, et al. Cervical cancer in women with comprehensive health care access: attributable factors in the screening process. J Natl Cancer Inst. 2005; 97:675-83.

[6] Janerich DT, Hadjimichael O, Schwartz PE, Lowell DM, Meigs JW, Merino MJ. et al. The screening histories of women with invasive cervical cancer, Connecticut. Am J Public Health. 1995; 85:791-4.

[7] US Census data, 2012 population estimates based on 2010 census data

[8] Centers for Disease Control and Prevention Online. "Hysterectomy Surveillance" --- United States, 1994,1999, 2002. <http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5105a1.htm. > reports from 1994 - 99 = 3,525,237 women had a historectomy; Wright JD et al. Obstet Gynecol. 2013 Aug;122(2 Pt 1):233-41 reports from 1998 - 2010 approx. 7,438,452 women had a hysterctomy. (Estimated ~11 million US women have a hysterectomy or approximately 11.3% of women over 30); Centers for Disease Control and Prevention. HIV Surveillance Report 2011. Vol. 23. <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/. Published February 2013. Accessed 8/12/13. (167.5 per 100,000 women or 0.17%)

[9] Behavioral Risk-Factor Surveillance System, Prevalence and Trend Data 2012. Women aged 18+ who have had a pap test within the past 3 years

eAppendix 4. One-Way Sensitivity Analysis

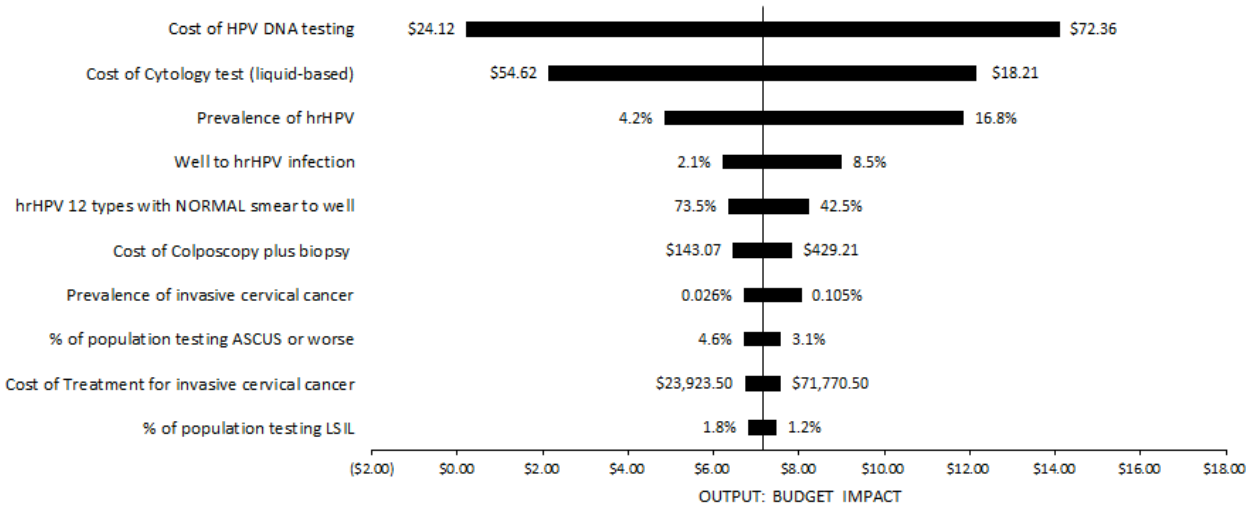
Results of the 1-way sensitivity analysis are shown in **eAppendix 4 Figure**, with the widest bar representing the most influential parameter on the model results and vice versa. The x-axis represents the cost differential between HPV primary screening at 3 years and the comparator. The top 10 inputs with the greatest impact on incremental cost are displayed.

The analysis revealed that the difference in cost per screened woman between cytology every 3 years and HPV primary screening 3-year intervals was most sensitive to cost of HPV testing, cost of cytology, the prevalence of HPV and the rate of HPV infection. Setting the cost of the HPV test equivalent to cytology ($36.41 for either test), results in a budget impact of $3.74, due to increased treatment cost. When comparing co-testing with and without genotyping at 3-year intervals to HPV primary screening at 3 years, the most impactful variable on the budget impact was cost of cytology. Even if cytology is performed at no cost, co-testing at 3 years leads to a slightly higher cost per screened woman (+$2.03) due to the increased cost of diagnosis (colposcopies performed).

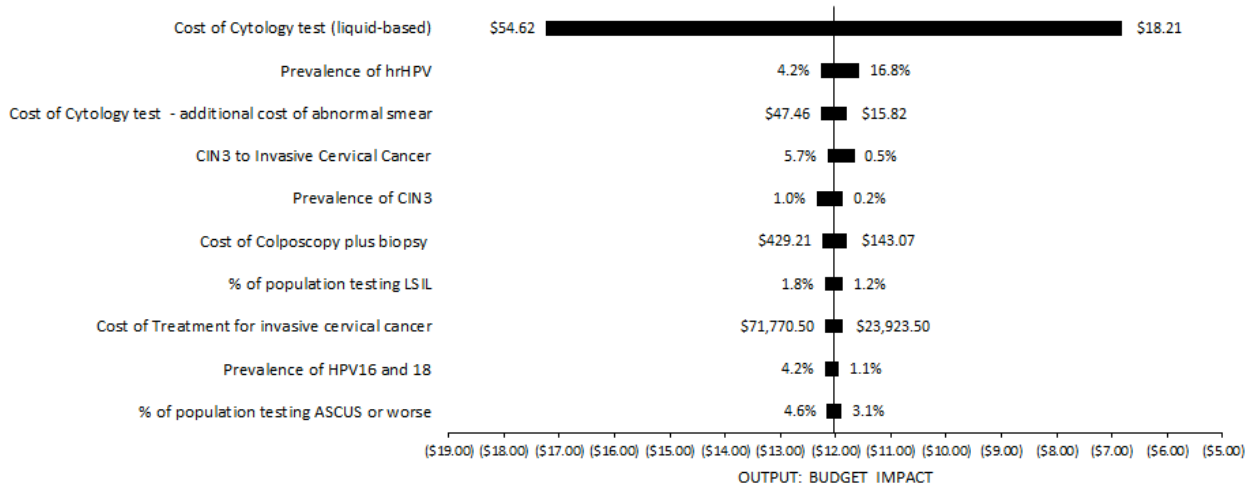
When comparing a HPV screening at 3 year vs co-testing with and without genotyping at a 5-year time horizon, the same parameters were impactful, with the addition of the cost of office visits, which had the largest impact on the cost difference. For office visits that cost more than the modeled value of $72.36, HPV primary screening every 3 years may move from being $11.81 more per screened woman to $15.80 (at $109.22/visit) more per screened woman. These may be important considerations for payers when creating reimbursement policies related to screening programs.

Figure. Tornado Diagrams

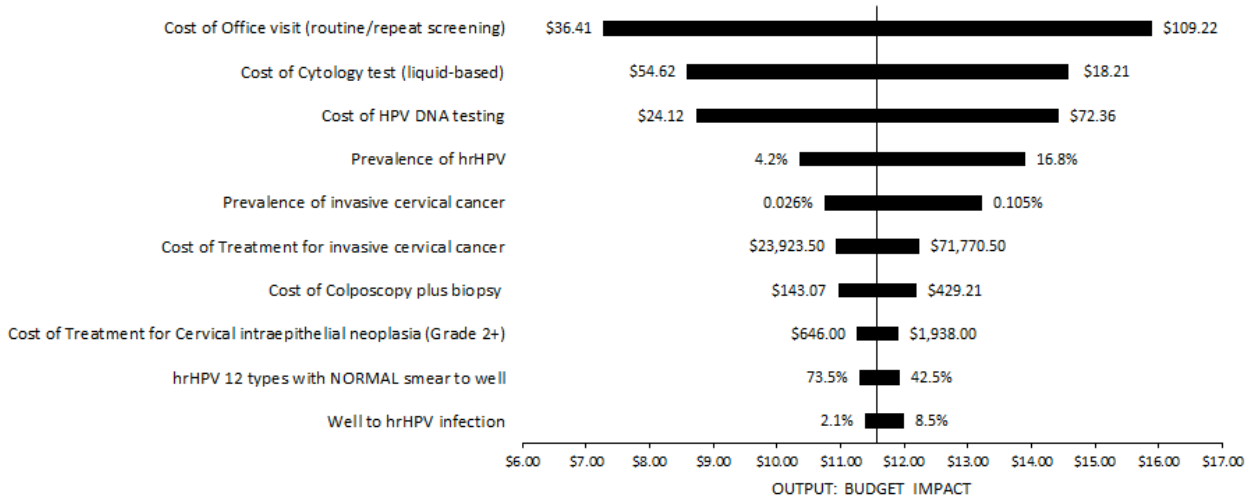
A. HPV With GT (3 years) Versus Cytology (3 years)



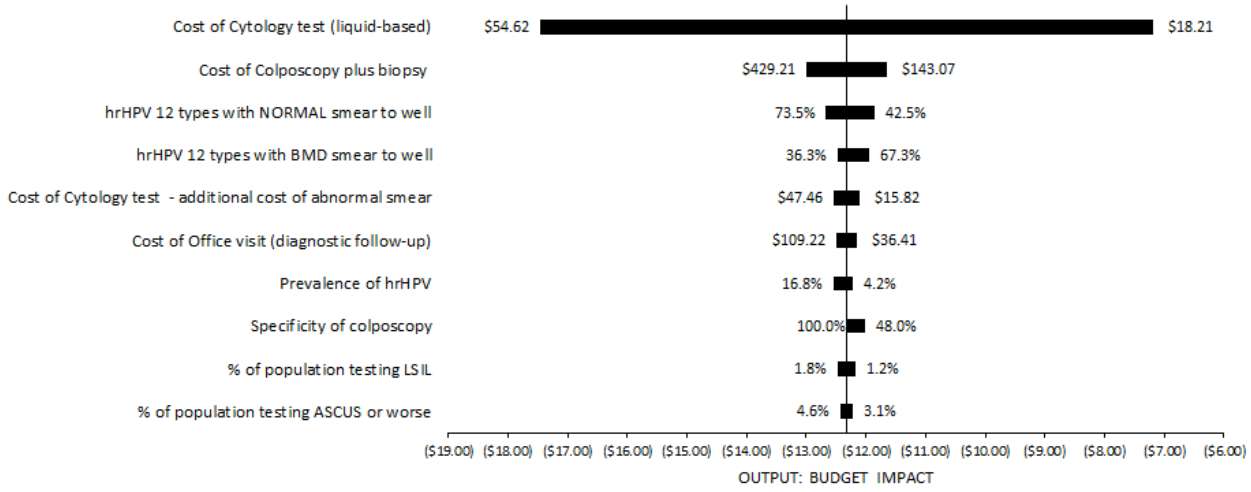
B. HPV With GT (3 years) Versus Co-Testing (3 years)



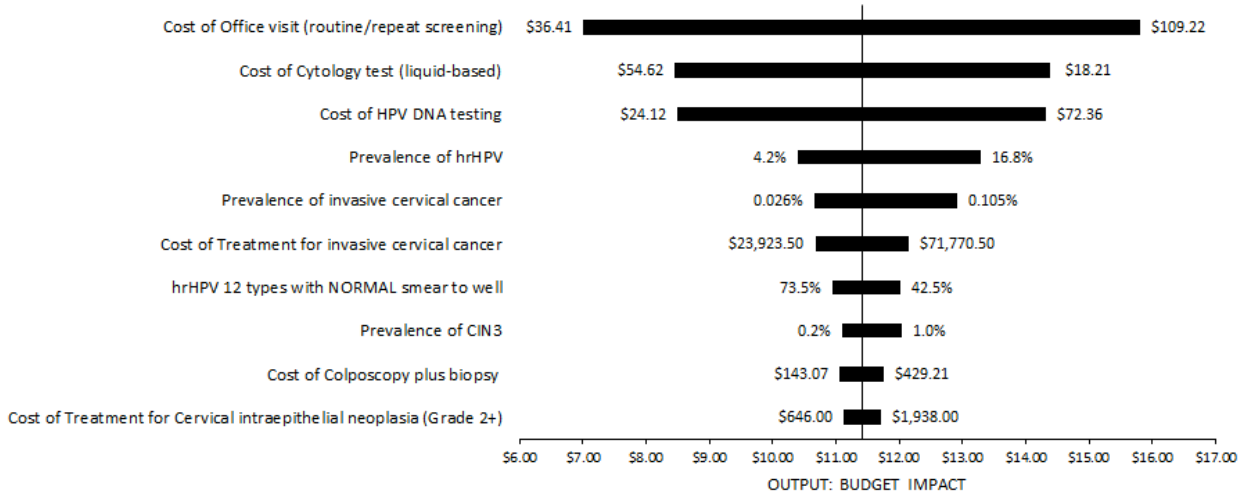
C. HPV With GT (3 years) Versus Co-Testing (5 years)



D. HPV With GT (3 years) Versus Co-Testing With GT (3 years)



E. HPV With GT (3 years) Versus Co-Testing With GT (5 years)

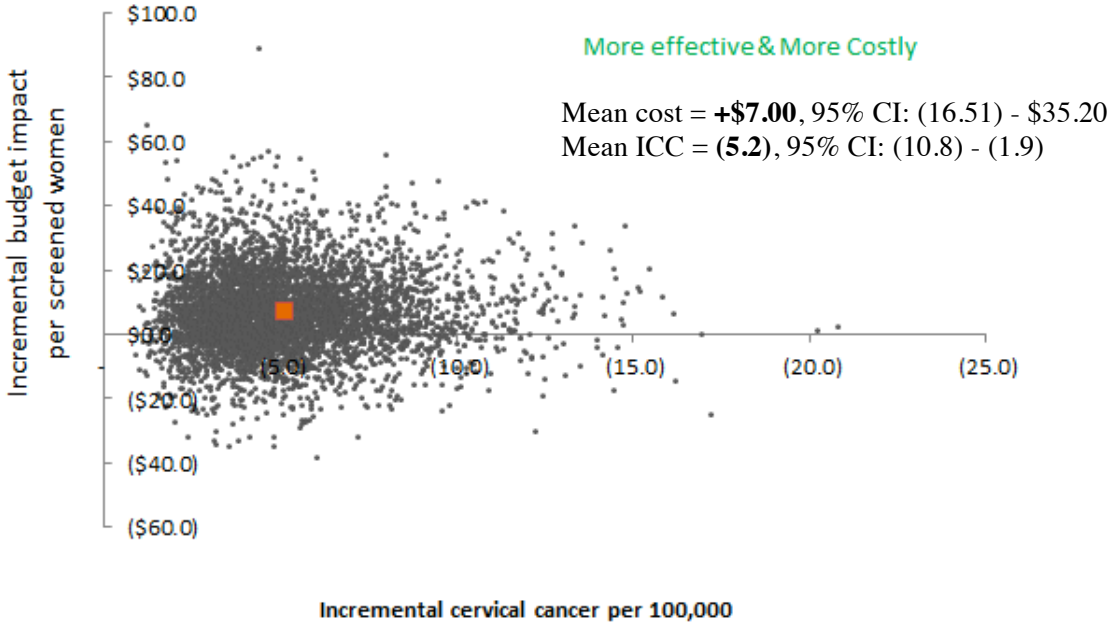


eAppendix 5. Probabilistic Sensitivity Analysis

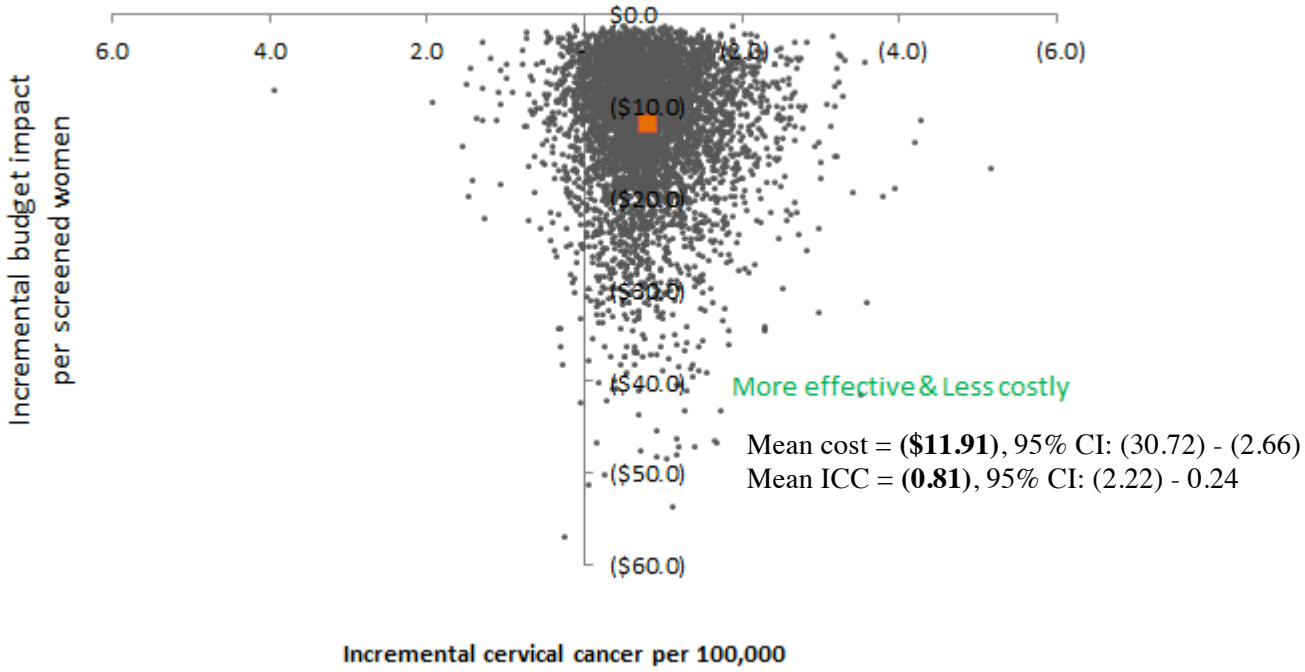
The cost effectiveness planes for the 5,000 simulations are shown in **eAppendix 5 Figure**. The x-axis represents incremental effectiveness of HPV primary screening every 3 years, measured as cervical cancers avoided. The y-axis represents incremental cost of implementing HPV primary screening every 3 years, measured as the cost per women screened. The area to the right of the vertical is clinically beneficial, and above the horizontal, cost-increasing.
The PSA shows uncertainty around the efficiency of the screening strategies. The precision for sensitivity studies will always be less than that of specificity, simply because of the smaller number of true positives relative to screen negatives. Because most women screen negative, it is important to consider the cost of the screening approach. For HPV primary screening versus co-testing scenarios, the detection of true positives is negligible; however the cost difference is nearly two-fold.

Figure

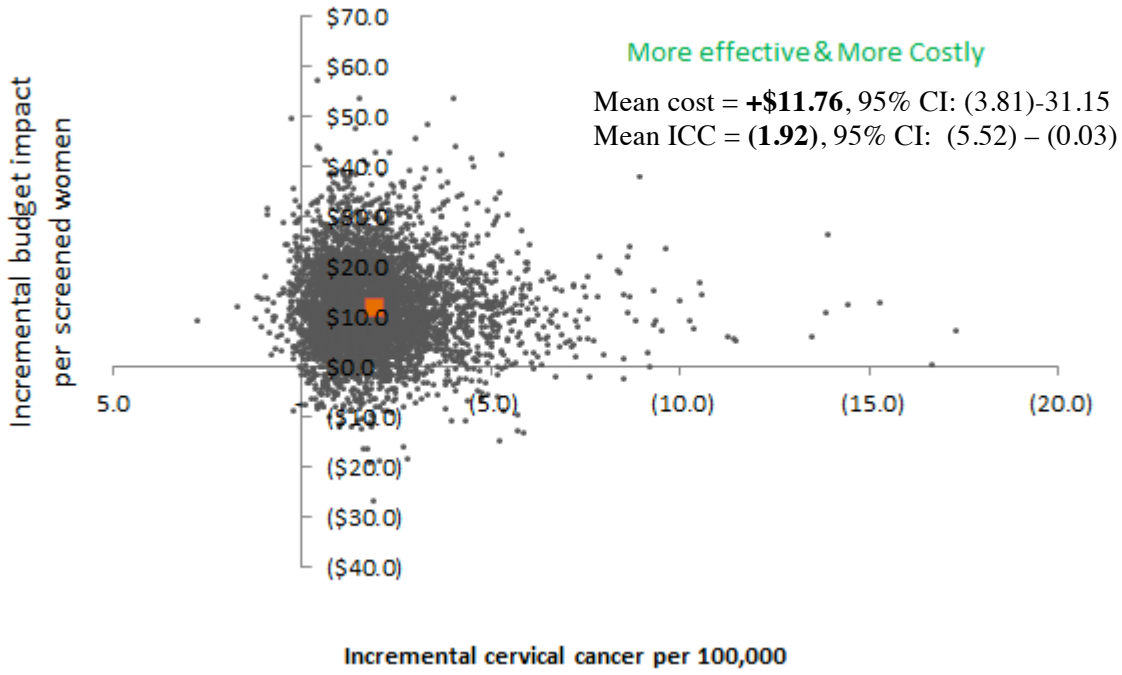
A. HPV With GT (3 years) Versus Cytology (3 years)



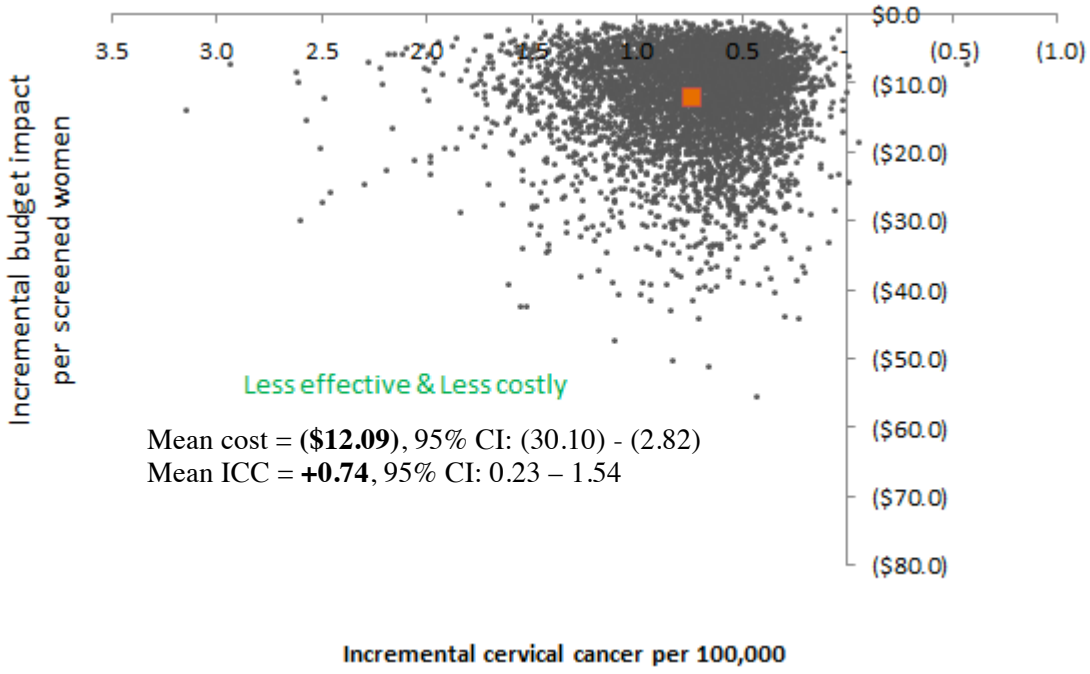
B. HPV With GT (3 years) Versus Co-Testing (3 years)



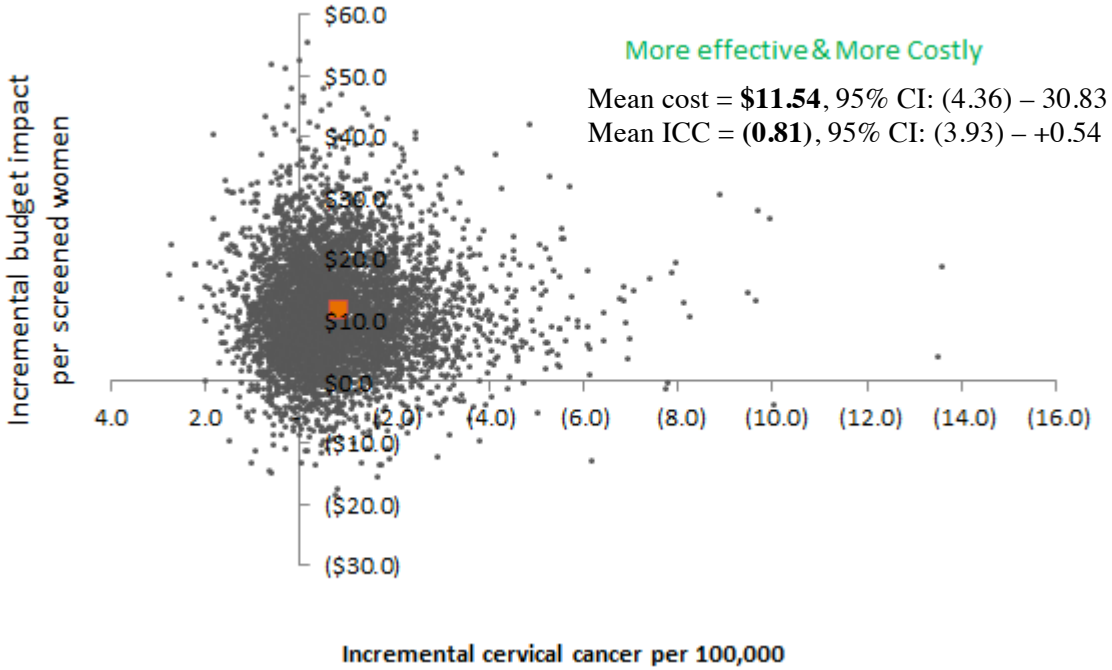
C. HPV With GT (3 years) Versus Co-Testing (5 years)



D. HPV With GT (3 years) Versus Co-Testing With GT (3 years)



E. HPV With GT (3 years) Versus Co-Testing With GT (5 years)



eAppendix 6. External Validation of Model Results

Validation using Ronco et al (2008) data: Modelled results were compared to Ronco et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial. *Lancet Oncol.* 2010;11:249-257, a large population based randomized control trial in which women aged 25 to 60 years were randomly assigned to receive cytology only or HPV with reflex cytology. Two rounds of screening took place; patients who did not attend repeat screening within 2 years were invited to a new screening round. In order to best mimic the protocol in the study within the bounds of the model, the model compares cytology only with retesting at 12 months and an interval of 2 years with HPV reflex cytology with the retest at 12 months and an interval of 2 years.

The comparison of relative detection rates for the model and Ronco et al (2010) are shown in the table below:

Detected CIN2, CIN3 and ICC	Cytology only repeat at 2 years (A)	HPV with reflex cytology repeat at 2 years (B)	Relative Detection, Modelled results (=B/A)	Relative Detection, Ronco et al results. Table 3. Women 35-60
Screening Round 1	193,480	344,524	1.78	1.94 (1.40-2.68)
Screening Round 2	99,522	91,091	0.92	0.74 (0.34-1.62)
Total CIN2, CIN3 and ICC	293,002	435,615	1.49	1.68 (1.25-2.26)

Conclusion: Model results align with the Ronco et al. study and fall within 95% confidence interval reported. HPV screening detects more pre-cancer and cancer in round 1, resulting in less CIN and ICC in round 2.

Validation using US SEER reported incidence of cervical cancer: Incidence of invasive cervical cancer calculated by the model for 2 common US screening strategies—cytology with reflex HPV (3 years) and co-testing (5 years)—was compared to published US data.

Comparison of US reported incidence to modelled incidence rate

US annual incidence of cervical cancer	12,900	[1]
Incidence attributed to 30-65 years	63%	[1],[2]
% attributed to screened population	50%	[3-6]
Total incidence of cervical cancer attributed to screened women aged 30-65 years	**4064**	
Model results for Cytology (3 years) annual ICC	5892	
Model results for Co-testing (5 years) annual ICC	4547	

[1] SEER data. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/ [based on November 2014 SEER data submission, posted to the SEER website: http://seer.cancer.gov/statfacts/html/cervix.html] Published April 2015. Accessed 6/18/15.
[2] Benard VB, Watson M, Castle PE, Saraiya M. Cervical carcinoma rates among young females in the United States. *Obstetrics and Gynecology*. 2012;120(5):1117–1123.
Cervical Cancer Rates Among Young Women in the United States. CDC website: http://www.cdc.gov/cancer/dcpc/research/articles/cervical-young-women.htm. Accessed 6/18/15.
[3] Sung HY, Kearney KA, Miller M, Kinney W, Sawaya GF, Hiatt RA. Papanicolaou smear history and diagnosis of invasive cervical carcinoma among members of a large prepaid health plan. *Cancer*. 2000;88:2283-2289.
[4] Kinney W, Sung HY, Kearney KA, Miller M, Sawaya G, Hiatt RA. Missed opportunities for cervical cancer screening of HMO members developing invasive cervical cancer (ICC). *Gynecol Oncol*. 1998;71:428-430.
[5] Leyden WA, Manos MM, Geiger AM, Weinmann S, Mouchawar J, Bischoff K. et al. Cervical cancer in women with comprehensive health care access: attributable factors in the screening process. *J Natl Cancer Inst*. 2005;97:675-683.
[6] Janerich DT, Hadjimichael O, Schwartz PE, Lowell DM, Meigs JW, Merino MJ. et al. The screening histories of women with invasive cervical cancer, Connecticut. *Am J Public Health*. 1995;85:791-794.

Conclusion: Model results for the calculated incidence of cancer align with reported US data. The model may be slightly over predicting the incidence of ICC however the results are highly sensitivity to the rate of progression from CIN3 to ICC. This probability of progressing from CIN3 to ICC untreated is a difficult input to source, since studies of this kind would be unethical. The model input was based on the best available data and consistent with other published models. Alternatively, actual screening intervals may differ from the 3 and 5 years recommended for cytology and co-testing, respectively.

Validation using Wright et al 2014 data: Model results were compared to Wright et al. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. *Gynecol Oncol*. 2015;136(2):187-97, results from ATHENA 3-year follow-up phase. The longitudinal strategy performance on efficiency was compared to model results in the table below:

Women ≥30 years	Number of detect cases year 1-3 **[A]**	Number of missed cases year 1-3 **[B]**	Sensitivity of strategy year 1-3 **[A]/[A+B]**	No. colposcopies to detect 1 case (95% CI)
Cytology (Wright Table 3)	185	192	**49%**	**7.0** (6.1-8.0)
Cytology reflex HPV (model results)	244,629	188,149	54%	6.4
Hybrid strategy (Wright, Table 3)	299	78	**79%**	**8.2** (7.4-9.2)
Co-testing (model results)	346,463	74,977	82%	8.2
Primary HPV (Wright, Table 3)	299	78	**79%**	**8.4** (7.6-9.4)
Primary HPV (model results)	344,410	70,027	83%	7.7

Conclusion: Model results for the sensitivity of the screening strategy align with reported ATHENA data. The number of colposcopies to detect 1 case of cancer are within the 95% CI reported by Wright et al.