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Research Article

Revisiting the Cost-Effectiveness of HPV Co-Testing Versus Primary HPV Testing for Cervical Cancer Screening

Jeffrey D Miller[1*], Adrian Vilalta[2], Kathleen A Troeger[3]

[1]IBM Watson Health, Cambridge MA, USA

[2]Hologic, Inc., San Diego, CA, USA

[3]Hologic, Inc., Marlborough, MA, USA

[*]**Corresponding author:** Jeffrey D Miller, IBM Watson Health, 75 Binney St, Cambridge, MA 02142, USA, Email: jffmill@us.ibm.com

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Abstract

Objectives: Consensus U.S. cervical cancer screening guidelines recommend women aged 30–65 years should be screened: (1) every 5 years with high-risk HPV testing alone; or (2) every 5 years with Pap and high-risk HPV co-testing; or (3) every 3 years with Pap alone. However, nearly 1-in-5 cancers (18.6%) are missed by HPV testing alone and 12.2% of cancers are missed by Pap testing alone. Hence, co-testing is the preferred screening method, but the cost implications are not fully known. For deeper understanding, we performed updated clinical-economic comparisons of cervical cancer screening with co-testing versus primary HPV from a U.S. perspective.

Methods: A health state transition (Markov) model with one-year cycling was previously developed using epidemiologic, clinical, and economic data from healthcare databases and published literature. After updating the model, it was used to perform simulations of women receiving either 3-year or 5-year interval cervical cancer screening with either co-testing or HPV primary, starting from age 30 years and running up through age 64 years. Outcomes included total and incremental differences in costs, number of referral colposcopies (true and false positive), invasive cervical cancer (ICC) cases, ICC deaths, and quality-adjusted life years (QALYs) for cost-effectiveness calculations.

Results: In the 3-year and 5-year screening interval scenarios, per-patient cumulative costs of screening and management over 35 years with co-testing versus HPV primary led to cost savings of $15 and $217, respectively. These cost saving resulted from fewer referral colposcopies, fewer ICC cases, and fewer ICC deaths. Co-testing also conferred more QALYs. Cost-effectiveness calculations showed co-testing as the economically dominant screening strategy by simultaneously confers greater effectiveness (i.e., more QALYs) at lower cost compared with HPV primary. National average annual cost savings of $154 to $655 million could be realized if every woman in the U.S. was routinely screened with co-testing instead of HPV primary.

Conclusions: Model results demonstrate that cervical cancer screening with co-testing provides valuable clinical and economic outcomes when compared to primary HPV testing alone. These findings are relevant to healthcare payers and women's health policy advocates seeking cost-effective cervical cancer screening options.

Keywords: Cervical Cancer; Cervical Cancer Screening; Human Papillomavirus (HPV); Papanicolaou (Pap) Test; Primary HPV Test; Co-Test; Costs; Cost-Effectiveness; Economic Model

1. Introduction

Cervical cancer was once one of the most common causes of cancer death for American women, but incidence and mortality of cervical cancer has been steadily decreasing over the past several decades, largely due to routine screening with Papanicolaou (Pap) cytology testing and human papillomavirus (HPV) detection testing [1]. Still, cervical cancer remains a formidable threat to the health of women, with estimation that about 13,800 new cases of invasive cervical cancer are diagnosed and about 4,300 women die from cervical cancer in the U.S. each year [1]. Consensus U.S. cervical cancer screening guidelines recommend women aged 30–65 years should be screened: (1) every 5 years with high-risk HPV testing alone; or (2) every 5 years with Pap and high-risk HPV co-testing; or (3) every 3 years with Pap alone [2-6].

However, nearly 1-in-5 cancers (18.6%) are missed by HPV testing alone and 12.2% of cancers are missed by Pap testing alone [2]. Because of its greater sensitivity, co-testing (i.e., Pap test plus HPV test together) is a preferred, standard-of-care screening method for women aged 30 to 65 years of age, as this combination of tests identifies more precancer and cancer cases than either test alone [2, 7-11]. Costs and cost-effectiveness and other concepts of economic value also are important factors in making recommendations for who should be screened and how often [12-14]. An effective way to analyze and comprehend the magnitude of the benefits and harms associated with different cervical cancer screening choices over a woman's lifetime is through modeling [13, 15, 16], especially in today's cost-conscious healthcare environment [12-14, 17]. Health economic modeling is a methodology commonly used to measure and establish the clinical and economic value, as well as financial impact, of pharmaceuticals and healthcare technologies such as cervical cancer screening.

A previously published modeling study [18] showed that reflex cytology co-testing with genotyping has the potential to provide improved clinical and economic outcomes when compared with HPV primary with genotyping. Specifically, results from this study showed that co-testing provides superior clinical outcomes compared with HPV primary and at lower cost, with conclusion that co-testing is the more cost-effective cervical cancer screening strategy compared with HPV

primary.

The objective of the present study was to revisit the previous modeling study and to make specific revisions to the health economic model, including updating the cost input parameters, modifying the screening age range to include women aged 30-64 years to better match current consensus guidelines, and bringing an alternative 5-year screening interval scenario to the forefront to pivot comparisons with the 3-year screening interval scenario, as previously modeled. Using the revised model, we performed a new set of analyses comparing the clinical and economic outcomes of co-testing versus HPV primary for cervical cancer screening and tender the results here for consideration by healthcare decision makers and policy analysts.

2. Materials and Methods

Building off the previously developed cost-effectiveness model and published paper [18] (available via open access, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4900245/), we made some specific revisions to the model parameters. First, we derived real-world estimates for all of the model's cost input parameters (except for invasive cervical cancer [ICC] treatment, which is still based on SEER–Medicare linked data [19]) from the *IBM® MarketScan® Commercial and Medicare Supplemental Databases* [20]. Inflation adjustments were performed where necessary using the Medical Care component of the U.S. Consumer Price Index (CPI) [21]. The modified cost input parameters are summarized in Table 1.

Parameter	**Unit Costs (2020 USD)**	**Reference**
Treatment of CIN2 or CIN3	$1,374.85	[20]
Colposcopy plus biopsy	$380.14	[20]
Cytology	$47.73	[20]
HPV hr genotyping	$57.94	[20]
HPV hr pooled test	$57.94	[20]
Office visit (routine/repeat screening)	$329.02	[20]
Treatment of ICC (initial)	$72,672	[19]
Treatment of ICC (continuing)	$1,910	[19]
Treatment of ICC (terminal)	$157,962	[19]

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

Table 1: Updated Model Cost Parameters.

Next, we a re-scaled the screening age range to focus on women aged 30-64 years to better match current consensus guidelines for cervical cancer screening. Finally, whereas the previously-published modeling analyses focused on 3-year screening intervals, we brought an alternative 5-year screening interval scenario (which aligns with consensus guidelines) to the forefront to conduct analyses side-by-side with the 3-year screening interval scenario. Other than these changes, the model structure and parameters, including test performance (i.e., sensitivity and specificity), disease progression/regression rates and all other underlying clinical data, as well as health state utilities, remain exactly as before and can be referred to in the

previous study publication.

Structurally, the updated model remains as a health state transition (Markov) model with 1-year cycling, now operating in TreeAge Pro Healthcare 2020 (TreeAge Software, Inc., Williamstown, Massachusetts, USA), using epidemiologic, clinical, and economic data from healthcare databases and published literature. Keeping with the previous study, the updated model performs clinical-economic comparisons of co-testing and HPV primary at the per-patient level and also assess select outcomes in context of a hypothetical cohort of one million 30-year-old screened women. Clinical outcomes and costs were simulated from ages 30 through 64 years, with women cohorts screened once every 3 years or once every 5 years. Differences in outcomes between the two screening strategy scenarios were accumulated annually across each cohort's life within the 35-year simulation timespan.

Model outcomes included total and incremental differences in costs, number of colposcopies (disagg-regated by true and false positive status), ICC cases, ICC deaths, and quality-adjusted life years (QALYs) for cost-effectiveness calculations. We also examined the cost-effectiveness of each screening strategy, calculated as an incremental cost-effectiveness ratio (ICER) with a cost-per QALY metric. We defined an ICER threshold of US$50,000 per QALY as good value for a U.S. payer, which has been described elsewhere [22-24]. As an additional model outcome, we projected the potential annual economic impact of each screening strategy on the total U.S. population by running the model for individual cohorts in 5-year increments (e.g., starting at ages 30 for 35 years, age 35 for 30 years, age 40 for 25 years, etc.) to reflect the annual impact that could be expected if either screening scenario was implemented across a cross-section of the U.S. population.

3. Results

3.1 Evaluation of clinical outcomes and costs

Results of the model analyses comparing co-testing with HPV primary are shown in Table 2. In the 3-year screening interval scenario, per-patient cumulative costs of screening and management over 35 years totaled $4,824 for co-testing (comprising $3,636 in screening costs and $1,188 in diagnosis and treatment costs), and $4,839 for HPV primary (comprising $3,353 in screening costs and $1,486 in diagnosis and treatment costs). The lower cost associated with co-testing compared to HPV primary translates as an overall savings of $15. As would be expected, total costs in the 5-year screening interval scenario were smaller, principally due to less frequent screening, although the incremental difference between the two screening strategies was substantially larger.

In the 5-year screening interval scenario, 35-year cumulative costs of screening and management for each patient totaled $3,651 for co-testing (comprising $2,317 in screening costs and $1,334 in diagnosis and treatment costs), and $3,868 for HPV primary (comprising $2,135 in screening costs and $1,733 in diagnosis and treatment costs). The lower cost associated with co-testing compared to HPV primary translates as an overall savings of $217.

Outcome	Co-testing	HPV Primary	Net Difference[a]
3-Year Screening Scenario			
Colposcopies[b]	1.9960	1.9995	-0.0035
True positive	0.1234	0.1182	0.0052
False positive	1.8727	1.8812	-0.0085
ICC cases per 10,000	53.84	74.28	-20.44
ICC deaths per 10,000	19.46	37.58	-18.12
Lifetime QALYs	21.5519	21.5325	0.0194
Screening costs	$3,636	$3,353	$283
Diagnosis and treatment costs	$1,188	$1,486	-$298
Total costs	$4,824	$4,839	-$15
ICER[c]			-$773 (Co-testing dominant)[d]
5-Year Screening Scenario			
Colposcopies[b]	1.2684	1.2659	0.0025
True positive	0.1128	0.1060	0.0068
False positive	1.1556	1.1599	-0.0043
ICC cases per 10,000	90.04	117.19	-27.15
ICC deaths per 10,000	31.46	57.44	-25.98
Lifetime QALYs	21.5346	21.5090	0.0256
Screening costs	$2,317	$2,135	$182
Diagnosis and treatment costs	$1,334	$1,733	-$399
Total costs	$3,651	$3,868	-$217
ICER[c]			-$8,477 (Co-testing dominant)[d]

ICC, invasive cervical cancer; *ICER*, incremental cost-effectiveness ratio; *QALY*, quality-adjusted life-year.

[a] Net difference = Co-testing − HPV primary.

[b] Sum of true positive and false positive colposcopies may not exactly equal the total number of colposcopies due to rounding.

[c] ICER = ΔCost / ΔQALY.

[d] Dominant means that co-testing simultaneously confers more QALYs at less cost, relative to HPV primary.

All values reported as per woman screened except where noted.

Table 2: Comparative Outcomes, Costs, and Cost Effectiveness.

In the 3-year screening interval scenario, co-testing resulted in a slight decrease in number of referral colposcopies per woman compared with HPV primary (1.9960 vs 1.9995, respectively), which projects as 3,500 fewer colposcopies in a cohort of one-million screened women.

Similarly, in the 5-year screening interval scenario, co-testing resulted in a slight decrease in referral colposcopies per woman compared with HPV primary (1.2684 vs 1.2659, respectively), representing 2,500 fewer colposcopies in the one-million-woman cohort. In both scenarios, co-testing resulted in more true positive

colposcopies per woman compared with HPV primary and fewer false positive colposcopies, with implications that there would be 5,200−6,800 more true positive colposcopies and 4,300−8,500 fewer false positive colposcopies across an entire million-woman screened cohort.

Compared with co-testing, HPV primary testing in the 3-year screening interval scenario was estimated to result in as many as 20 additional ICC cases per 10,000 women screened and 18 additional ICC deaths per 10,000. Results of the 5-year scenario were similar, with HPV primary testing estimated to result in as many as 27 additional ICC cases per 10,000 and 26 additional ICC deaths per 10,000. The model also calculated a greater number of QALYs per women screened for co-testing in both the 3-year and 5-year screening interval scenarios, with the respective incremental differences ranging from 0.0194 to 0.0256 QALYs.

3.2 Cost-Effectiveness

Constructing ICERs using the incremental change in total costs and incremental change in QALYs described above and presented in Table 2, results demonstrate that co-testing simultaneously confers greater effectiveness (i.e., more QALYs) at lower cost compared with HPV primary, and, therefore, co-testing is the *economically dominate* screening strategy [25].

3.3 Nationwide projection

Model results were used to calculate a projection to demonstrate the comparative financial impact at the U.S. national level, assuming every woman in the U.S. aged 30-64 years would adhere to a 3-year or 5-year screening interval that would be hypothetically implemented now (Table 3).

Using a cross section of the total U.S. female population of 72.3 million women between 30 and 64 years of age [26], the model predicts an average annual cost savings of $154 to $655 million respectively in the 3-year and 5-year screening interval scenarios where women are screened up to age 65.

Age (years)	Cumulative Cost Per Woman to Age 65 Years			Female U.S. Population	Average Annual National Cost[a]		
	Co-testing	HPV Primary	Cost Savings[b]		Co-testing	HPV Primary	Cost Savings[b]
3-Year Screening Interval Scenario							
30–34	$4,824	$4,839	($15)	9,965,599	$1,373,544,274	$1,377,815,245	($4,270,971)
35–39	$4,569	$4,631	($62)	10,137,620	$1,543,959,526	$1,564,910,607	($20,951,081)
40–44	$4,117	$4,185	($68)	10,496,987	$1,728,643,819	$1,757,195,624	($28,551,805)
45–49	$3,587	$3,648	($61)	11,499,506	$2,062,436,401	$2,097,509,894	($35,073,493)
50–54	$2,919	$2,972	($53)	11,364,851	$2,211,600,005	$2,251,755,811	($40,155,807)
55–59	$2,232	$2,262	($30)	10,141,157	$2,263,506,242	$2,293,929,713	($30,423,471)
60–64	$1,368	$1,365	$3	8,740,424	$2,391,380,006	$2,386,135,752	$5,244,254
Total				**72,346,144**			**($154,182,374)**
5-Year Screening Interval Scenario							
30–34	$3,651	$3,868	($217)	9,965,599	$1,039,554,341	$1,101,341,055	($61,786,714)
35–39	$3,573	$3,833	($260)	10,137,620	$1,207,390,542	$1,295,249,915	($87,859,373)
40–44	$3,231	$3,475	($244)	10,496,987	$1,356,630,600	$1,459,081,193	($102,450,593)
45–49	$2,790	$2,999	($209)	11,499,506	$1,604,181,087	$1,724,350,925	($120,169,838)
50–54	$2,284	$2,448	($164)	11,364,851	$1,730,487,979	$1,854,743,683	($124,255,704)
55–59	$1,666	$1,769	($103)	10,141,157	$1,689,516,756	$1,793,970,673	($104,453,917)
60–64	$911	$942	($31)	8,740,424	$1,592,505,253	$1,646,695,882	($54,190,629)
Total				**72,346,144**			**($655,166,768)**

[a] Costs for each age bracket are adjusted by maximal number years of screening (e.g., 30–34 years = 35 screening years, 35–39 years = 30 screening years, 40–44 years = 25 screening years, etc.).

[b] Cost savings = Co-testing cost – HPV primary cost.

Table 3: Cost Savings Projected to the National Level.

4. Discussion

The fundamental goal of cervical cancer screening is to prevent morbidity and mortality from cervical cancer through accurate detection and timely treatment of precursor lesions of the cervix [8, 27]. Co-testing with combined Pap and HPV testing fits well into this cervical cancer screening paradigm. However, comparative advantages and disadvantages of co-testing versus HPV primary screening in real-world practice remains contentious. The lack of dedicated clinical studies to guide good decision making about the risks and benefits of available cervical cancer screening modalities has been particularly unhelpful, but maybe the biggest hurdle comes from the fact that there is no common agreement between what is acceptable and unacceptable balance of benefits and harms in cervical cancer screening [28]. Moreover, real-world screening practices are subjective and frequently diverge from the guidelines [29, 30]. For example, some clinicians reject the 5-year co-testing interval and repeat co-testing every 3 years

(or even more frequently in some cases) and start screening their patients at younger ages, driven by greater reassurance for protecting their patients from cervical cancer, with or without acknowledgement about the extra costs and additional procedures required [15, 31, 32]. Recently, Kaufman and colleagues [7] assessed the clinical results of co-testing performed over nine years in 13,633,071 women, concluding that co-testing with liquid-based cytology (LBC) combined with HPV testing is superior for detection of cervical cancer in women 30 years and older, compared with LBC or HPV testing alone. More real-world studies like this will prove crucial for building consensus, especially if comparative costs also can be factored into the deliberation.

Result from this modeling analysis clarify several things about the comparative clinical-economic value of co-testing versus HPV primary. The model predicts 23%−28% reduction in ICC cases and 45%−48% reduction in ICC deaths over 35 years with co-testing compared with HPV primary. Not only is this confirmation that co-testing is clinically advantageous compared with HPV primary screening, it also explains how co-testing can be an economically advantageous screening strategy. Analysis results indicate that among women 30 to 64 years of age, cervical cancer screening using co-testing either at 3-year or 5-year intervals leads to cost savings of $15 to $217. Further, the model results demonstrate that co-testing is a cost-effective screening strategy. In fact, co-testing with either 3- or 5-year re-screening intervals lands in the coveted position of being the *economically dominant* alternative to HPV primary. This means that co-testing confers better clinical benefit (whether measured as fewer incidences of cervical cancer and cancer deaths, or by the gain in life expectancy or QALYs) and at lower cost than HPV primary—and this achievement is realized without increasing the real and perceived harms of colposcopies. A better sense of the magnitude of the clinical and economic benefits associated with shortening the co-testing screening interval and initiating co-testing at an earlier age is achieved in the projected national estimates. Although it would be unrealistic to expect that every woman in the U.S. would be regularly screened with one modality or the other, the projection gives perspective at the larger population level of how seemingly small differences accrued over the many tests in the course of a woman's life can then magnify across the many millions of women in the U.S. population who should be screened [15]. We estimated cost savings of co-testing ranging from $15 to $217 over 35 years, which might seem meager. However, considering that there are 72.3 million women between the ages of 30 and 64 years in the U.S. [26] the national cost savings would average an astounding $154−$655 million per year.

Cost comparisons and cost-effectiveness analyses of cervical cancer screening from the U.S. perspective have started to be explored by other researchers within the past 5 years, [14, 33, 34] including the model and paper that were the precursor to the present study [18]. The analysis presented here has notable improvements over previous studies, including evaluating a cohort of women screened from age 30 years up to 65 years to more closely align with the age range recommended in consensus guidelines. Another improvement comes from using cost values derived from the *IBM® MarketScan® Commercial and Medicare Supplemental Databases* [20]. Consequently, results should more closely reflect real-world cervical cancer screening costs.

The most notable change made in the present analysis was to perform direct comparisons between 3-year and 5-year screening intervals for both co-testing and HPV primary. Although guidelines currently recommend a

five year screening interval for co-testing and HPV primary, this continues to be the subject of ongoing debate in the scientific community as data 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 [15, 35]. Results from our analysis confirm this. The debate over 3-year versus 5-year screening intervals has historic roots in the modeling analyses conducted by Kulasingam et al. [35] at the behest of the U.S. Preventive Services Task Force to inform its 2012 cervical cancer screening guidelines [36]. Additional modeling work was published in 2018 by Kim et al. [37] in support of the revised USPSTF guidelines [38]. Neither of these studies evaluated costs, so the cost estimates from our study will add a new dimension for consideration in the debate. The estimated incremental cost savings associated with co-testing under the 3-year screening interval scenario in the present study aligns closely with the previous study ($15 versus $39). Although 5-year screening intervals were not explored in the previous analysis, the cost savings estimated here in the 5-year scenario are dramatically larger— $217. Albeit, this cost savings would come at the expense of additional cervical cancer cases and cervical cancer deaths. Whether there is willingness to forego the $202 difference in cost savings between the 3-year and 5-year screening interval scenarios as a means to prevent these additional cancer cases and cancer deaths is relegated to conjectural debate and additional analytical exploration.

Some of the limitations of the model described in the previous publication [18] still stand true in this analysis. Our study was performed from the U.S. healthcare payer perspective and accounts for direct medical costs. Indirect or intangible costs—especially those borne by patients themselves as they pertain to out-of-pocket expenses, pain, psychosocial distress, future fertility and reproduction problems, etc. were not part of the calculations. For simplicity, our analyses were based on "guideline perfect" assumptions of 100% adherence to screening intervals and follow-up of screen-positive women; however, it is well documented that screening practice is not perfect and is quite variable across the U.S. 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. Moreover, the model still does not account for the impact of increasing rates of HPV vaccination. Finally, as was true before, this analysis is limited by the lack of long-term data regarding HPV primary screening, and there even greater need now for large-scale longitudinal studies are needed to determine the effectiveness of HPV primary screening strategies in U.S. women.

5. Conclusions

Results from this modeling analysis demonstrate that HPV co-testing provides valuable clinical and economic outcomes when compared to primary HPV testing alone, both at the patient level and also when aggregated to the national level where millions of women in the U.S. are urged to adopt and adhere to regular cervical cancer screening. These findings are relevant to U.S. healthcare payers and women's health policy advocates seeking cost-effective cervical cancer screening technologies. Results also should help inform future changes to cervical cancer screening guidelines as well as real-world screening practices.

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