Cost-Effectiveness of Primary HPV Testing, Cytology and Co-testing as Cervical Cancer Screening for Women Above Age 30 Years

Xian Wen Jin, MD, PhD[1], Laura Lipold, MD[2], Julie Foucher, BS[3], Andrea Sikon, MD[1], Jennifer Brainard, MD[4], Jerome Belinson, MD[5], Sarah Schramm, MA[6], Kelly Nottingham, MPH[6,7], Bo Hu, PhD[8], and Michael B. Rothberg, MD, MPH[1,6]

[1]Department of Internal Medicine, Cleveland Clinic, Cleveland, OH, USA; [2]Department of Family Medicine, Cleveland Clinic, Cleveland, OH, USA; [3]Cleveland Clinic Lerner College of Medicine, Cleveland Clinic, Cleveland, OH, USA; [4]Department of Pathology, Cleveland Clinic, Cleveland, OH, USA; [5]Department of Obstetrics and Gynecology, Cleveland Clinic, Cleveland, OH, USA; [6]Medicine Institute Center for Value Based Care Research, Cleveland Clinic, Cleveland, OH, USA; [7]Heritage College of Osteopathic Medicine, Ohio University, Athens, OH, USA; [8]Department of Quantitative Health Science, Cleveland Clinic, Cleveland, OH, USA.

BACKGROUND: Cervical cancer screening guidelines for women aged ≥30 years allow for co-testing or primary cytology testing. Our objective was to determine the test characteristics and costs associated with *Cytology*, *HPV* and *Co-testing* screening strategies.

MAIN METHODS: Retrospective cohort study of women undergoing cervical cancer screening with both cytology and HPV (Hybrid Capture 2) testing from 2004 to 2010 in an integrated health system. The electronic health record was used to identify women aged ≥30 years who had co-testing. Unsatisfactory or unavailable test results and incorrectly ordered tests were excluded. The main outcome was biopsy-proven cervical intraepithelial neoplasia grade 3 or higher (CIN3+).

KEY RESULTS: The final cohort consisted of 99,549 women. Subjects were mostly white (78.4 %), married (70.7 %), never smokers (61.3 %) and with private insurance (86.1 %). Overall, 5121 (5.1 %) tested positive for HPV and 6115 (6.1 %) had cytology ≥ ASCUS; 1681 had both and underwent colposcopy and 310 (0.3 %) had CIN3+. Sensitivity for CIN3+ was 91.9 % for *Primary Cytology*, 99.4 % for *Co-testing, and* 94.8 % for *Primary HPV*; specificity was 97.3 % for *Co-testing* and *Primary Cytology* and 97.9 % for *Primary HPV*. Over a 3-year screening interval, *Primary HPV* detected more cases of CIN3+ and was less expensive than *Primary Cytology*. *Co-testing* detected 14 more cases of CIN3+ than *Primary HPV*, but required an additional 100,277 cytology tests and 566 colposcopies at an added cost of $2.38 million, or $170,096 per additional case detected.

CONCLUSIONS: *Primary HPV* was more effective and less expensive than *Primary Cytology*. *Primary HPV* screening appears to represent a cost-effective alternative to *Co-testing*.

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INTRODUCTION

Cervical cancer is the fourth leading cause of cancer death in women worldwide, with an estimated 275,000 deaths each year.[1,2] Incidence of cervical cancer in the US has decreased >50 % because of the success of the Papanicolaou (Pap) test (cytology screening). As a result, cervical cancer mortality has also declined by half.[3] The American Cancer Society estimates 4100 cervical cancer deaths in the US in 2015, most due to lack of screening or follow-up from abnormal testing.[4]

Elucidation of the role of high-risk human papillomavirus (HPV) in cervical cancer pathogenesis has led to incorporation of HPV testing into primary screening strategies for women age 30 and older.[5] When cytology and HPV tests are used together (co-testing), sensitivity approaches 100 %,[6] and the 5-year risk of cervical intraepithelial neoplasia grade 3 or higher (CIN3+) after a negative co-test is far below that with negative cytology alone, supporting longer testing intervals.[7,8] For this age group, multiple organizations now recommend co-testing every 5 years as an alternative to cytology.[5,9–11] The American Cancer Society, The American Society of Colposcopy and Cervical Pathology (ASCCP) and the American Society of Clinical Pathology recommend co-testing as a "preferred" screening strategy,[5] although the appropriateness of this recommendation has been questioned.[12] The US Preventive Service Task Force (USPSTF) recommends cytology or co-testing as acceptable screening. Co-testing is more expensive, but estimates of cost-effectiveness are lacking in the US.[13]

Several studies support the use of primary HPV testing (HPV followed by cytology for positive HPV results) due to its high sensitivity and negative predictive value.[6,14–22] One systematic review suggests that co-testing has only marginal benefit over primary HPV testing, with significantly increased cost.[23] In 2014, the Food and Drug Administration (FDA) approved the cobas® HPV Test (Roche Molecular Systems) for primary screening in women age 25 and older, and an interim guidance panel of the ASCCP and the Society of Gynecologic Oncology (SGO) stated that high-risk HPV testing could be considered an alternative to guideline-recommended options.[24]

Despite FDA approval, a number of concerns remain. Some worry that primary HPV testing may not be sufficiently sensitive and cases will be missed, especially because it has not been studied in routine practice.[25] Many institutions do not use the cobas® Test and may be reluctant to change based on a single trial. Finally, the cost-effectiveness of primary HPV screening is unknown. To investigate the utility of primary HPV screening strategies in clinical practice, we compared the expected outcomes and cost of a *Primary HPV* strategy using the most widely used HPV test (Hybrid Capture 2) to those of *Co-testing* and *Primary Cytology* in an integrated health system.

METHODS

We conducted a retrospective cohort study of women ≥30 years of age who had co-testing with HPV DNA and cytology for primary cervical cancer screening in an integrated health system from 2004 to 2010. This study was approved by the Cleveland Clinic Institutional Review Board. Patients who had diagnostic tests incorrectly ordered as screening or whose HPV or cytology results were unsatisfactory or unavailable were excluded. The electronic health record (Epic® EHR) was queried to identify eligible patients and extract demographics. The primary outcome of histologically confirmed CIN3+ was chosen because it is reliably diagnosed,[26–28] has a low likelihood of regression[29,30] and is a surrogate for cancer.[7] A supplemental analysis was performed using the outcome of CIN2+.[6] CIN3+ was identified from the pathology reporting system (CoPath). HPV and cytology results were obtained through chart review. For women with CIN3+ lesions, the results of the co-test immediately preceding cervical biopsy were recorded. For women without histologically confirmed CIN3+ lesions, we recorded the results of the most recent co-test. To accurately determine prevalence, positive and negative predictive values, patients with abnormal screening tests who did not undergo colposcopy were identified and their outcomes assigned using multiple imputation.

Cytology specimens were analyzed by the ThinPrep Imaging System™ (Hologic). Results were reported according to the 2001 Bethesda System.[31] HPV status was determined utilizing Hybrid Capture 2 (Qiagen) as either positive or negative for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68.[32] HPV-16/HPV-18 genotypes were not distinguished from other genotypes.

Using HPV and cytology results, we modeled three primary screening strategies (Fig. 1) from the payer perspective. The first two, *Primary Cytology* and *Co-testing*, reflect current recommendations for women age 30 and older.[5,9,10,13] In the third strategy, *Primary HPV*, positive HPV results are followed by cytology, while negative HPV results prompt no testing for 5 years.

In the model, only patients with positive HPV and cytology ≥ atypical squamous cells of undetermined significance (ASCUS) are referred to colposcopy. Patients with positive HPV and normal cytology receive repeat co-testing in 1 year.

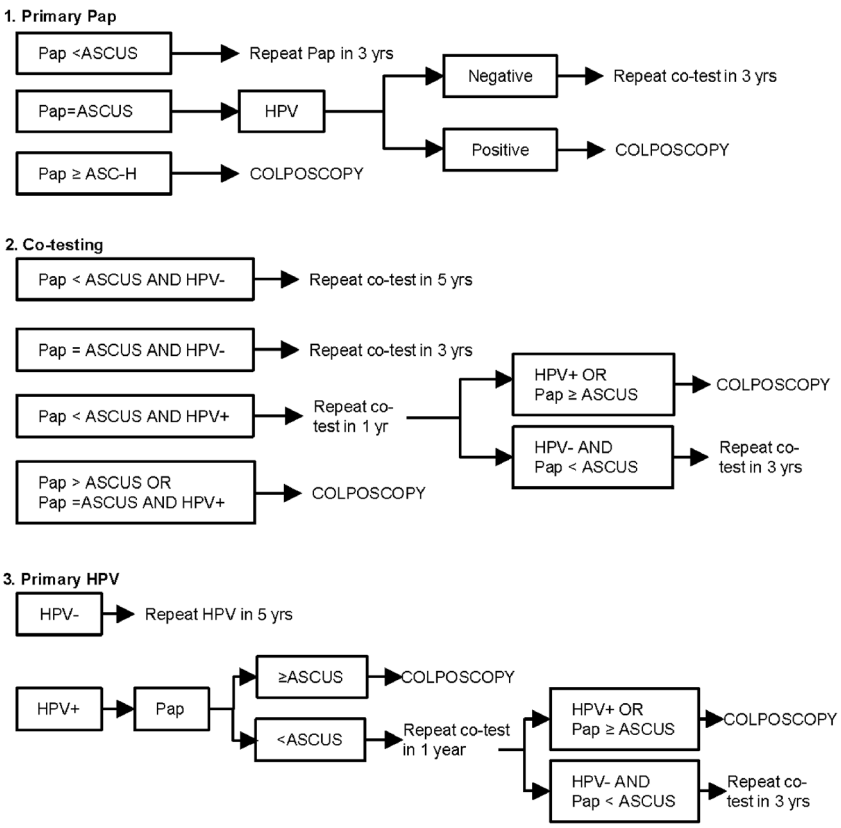

Figure 1 Screening strategies for primary cervical cancer screening adapted from the ASCCP Guidelines[11]. *ASCCP* American Society for Colposcopy and Cervical Pathology, *HPV* human papillomavirus, *ASCUS* atypical cells of undetermined significance

Patients remaining HPV positive or ≥ ASCUS at 1 year are referred to colposcopy. Referred patients who do not undergo colposcopy do not incur colposcopy costs and cannot have CIN3+ detected, even if present. Sensitivity, specificity and predictive values of the strategies were based on observed results, without imputation. To determine the costs associated with detection of a case of CIN3+ we performed a simulation based on the results of the recorded HPV test, cytology test and the known CIN3+ outcome. We assumed that all patients with a follow-up test would have CIN3+ detected if present. For patients who were HPV negative in the primary HPV strategy, or HPV negative and cytology negative in the co-test strategy, we assumed no further testing, and CIN3+ would not be detected, even if present. In reality, two of these women had additional testing (e.g., repeat cytology or HPV test in <3 years) and were found to have CIN3+, so no strategy detected all cases. To determine costs, we summed the number of HPV tests, cytology tests and colposcopies for each strategy over a 3-year interval and assigned costs using current Medicare National Facility Prices (eTable 1).[33] For *Co-testing* and *Primary HPV*, we multiplied the cost of the 5-year interval by 3/5. Office visit costs were not included because we assumed that testing would be conducted during an annual examination. For the *Primary Cytology* and *Primary HPV* strategies, we assumed that both HPV and cytology specimens would be collected but the secondary specimen would be processed only in the case of a positive primary result. Costs to store unprocessed cytology specimens could not be ascertained and were not included. The collection kit represents approximately 10 % of the cost of the test. In a sensitivity analysis, we varied the storage cost from 10 to 30 % of the cost of cytology. We estimated colposcopy costs based on a weighted average of Medicare prices for colposcopy procedure codes in our study population. This analysis was limited to one round of screening and did not include the cost of surveillance following colposcopy.

STATISTICAL ANALYSIS

Baseline characteristics were summarized as frequencies and percentages. Characteristics of patients who were referred and did or did not undergo colposcopy were compared using the chi-squared test. For referred patients who did not undergo colposcopy ($n = 375$), CIN3+ results were imputed based on a logistic regression model that used the observed CIN3+ results among the entire cohort as outcomes and baseline characteristics and HPV and cytology results as predictors. Results were imputed five times and summarized using Rubin's rule. Similar analyses were performed to impute CIN2+ results.

Prevalence of CIN2+/CIN3+ was estimated as percentages with 95 % confidence intervals. Test characteristics were estimated for the initial round of screening. Analyses were conducted using SAS 9.3 (Cary, NC) and R 3.0.2 (cran.r-project.org).

RESULTS

We identified 101,889 patients who met the inclusion criteria. We excluded patients with diagnostic testing ordered as screening ($N = 35$) and those with unsatisfactory or unavailable test results ($N = 2305$), resulting in a final cohort of 99,549 patients. Patient characteristics appear in Table 1.

Table 1 Demographics ($N = 99,549$)

	All		HPV +		CIN3+		CIN2+	
Characteristic	**N**	**%***	**N**	**%†**	**N**	**%†**	**N**	**%†**
Age								
30–39	28,819	28.9 %	2377	8.2 %	161	0.6 %	380	1.3 %
40–49	29,965	30.1 %	1423	4.7 %	62	0.2 %	164	0.5 %
50–59	25,401	25.5 %	879	3.5 %	29	0.1 %	79	0.3 %
≥60	15,364	15.4 %	442	2.9 %	17	0.1 %	38	0.2 %
Race								
White	78,076	78.4 %	3676	4.7 %	197	0.3 %	480	0.6 %
Black	13,234	13.3 %	982	7.4 %	50	0.4 %	128	1.0 %
Other	8239	8.3 %	463	5.6 %	22	0.3 %	53	0.6 %
Marital status‡								
Single/Widowed and age <50	19,041	19.3 %	1776	9.3 %	77	0.4 %	202	1.1 %
Married/domestic partner/widowed and age ≥50	69,662	70.7 %	2234	3.2 %	146	0.2 %	327	0.5 %
Divorced/separated	9782	9.9 %	1043	10.7 %	39	0.4 %	122	1.2 %
Smoking status‡								
Smoke/passive smoker	12,254	12.4 %	1131	9.2 %	61	0.5 %	140	1.1 %
Former smoker	25,836	26.2 %	1299	5.0 %	85	0.3 %	183	0.7 %
Never smoked	60,391	61.3 %	2621	4.3 %	122	0.2 %	336	0.6 %
Unknown	62	0.1 %	6	9.7 %	0	0.0 %	1	1.6 %
Insurance‡								
Medicaid	1050	1.1 %	113	10.8 %	10	1.0 %	28	2.7 %
Medicare	11,684	12.6 %	448	3.8 %	22	0.2 %	45	0.4 %
Private	79,735	86.1 %	3992	5.0 %	218	0.3 %	542	0.7 %
Self-pay	161	0.2 %	39	24.2 %	11	6.8 %	31	19.3 %

HPV human papillomavirus, CIN2+ cervical intraepithelial neoplasia 2 or worse, CIN3+ cervical intraepithelial neoplasia 3 or worse
**Percentages are with respect to the total sample size*
†Percentages are with respect to the sample size in the corresponding category of the characteristic
‡Missing data not reported

Subjects were mostly under age 60 (84.6 %), white (78.4 %), married (70.7 %), never smokers (61.3 %) and with private insurance (86.1 %). A total of 8836 patients (8.9 %) had a positive test by either HPV ($N = 5121$, 5.1 %) or cytology ($N = 6115$, 6.1 %). Of these, 1681 underwent colposcopy, and 310 (0.3 %) had CIN3+ lesions (Table 2). Both positive HPV and CIN3+ were more common among women who were younger, black, single and smokers. Additionally, 375 patients had positive cytology but did not undergo colposcopy. These patients were not different in age or marital status from those who underwent colposcopy; however they were more likely to be white, to smoke and to not have private insurance ($p < 0.001$) (eTable 2). Of these patients, we imputed 139 cases of CIN2+ and 74 cases of CIN3+. Eleven cancers were reported—two metastatic breast and nine cervical (1 squamous, 8 adenocarcinoma).

The incidence of CIN3+ by HPV and cytology status appears in Table 2. CIN3+ was more common with positive than negative HPV results (5.7 % vs. 0.02 %, $p < 0.001$). HPV-positive patients with abnormal cytology had high rates of CIN3+ (≥4.6 %). Of patients who were HPV negative, only those with cytology indicating ASC-H, HSIL and cancer had rates of CIN3+ >0.6 %. Only two HPV-negative patients with any other cytology result had CIN3+.

Test characteristics appear in Table 3. Sensitivity of *Co-testing* (99.4 %) was greater than for *Primary HPV* (94.1 %) and *Primary Cytology* (90.7 %). *Primary HPV* was slightly more specific (98.1 %) than the other strategies (both 97.6 %) and had the greatest positive predictive value (12.1 % vs. 9.6 % for *Primary Cytology* and 10.3 % for *Co-testing*). All strategies had negative predictive values exceeding 99.9 %.

Over a 3-year period, *Primary HPV* was the least expensive, detecting 294 cases of CIN3+ with 2422 colposcopies per 99,549 screened at a cost of $3.47 M. *Primary Cytology* detected nine fewer cases of CIN3+ but cost more. *Co-testing* detected 14 additional cases of CIN3+ than *Primary HPV* but would require 100,277 more cytology tests and 566 more colposcopies at an additional cost of $2.38 million, or $170,096 per case detected (Table 4). In sensitivity analysis, this marginal cost ranged from $166,864–$173,327 as the cost of the HPV test was varied from 50 to 150 % of the current Medicare National Facility Price (eTable 6). Increasing the cost of cytology made *Co-testing* even more expensive, whereas including costs for cytology storage in the *Primary HPV* strategy decreased the marginal cost of *Co-testing*. Varying the storage cost from 10 to 30 % of the cost of cytology produced marginal costs of $157,566 to $132,506. Results were similar for patients with CIN2+ (eTables 3–6).

Table 2 CIN3+ Incidence by Cytology and HPV Results

	CIN3+/HPV positive		CIN3+/HPV negative	
	Incidence	% (95 % CI)	Incidence	% (95 % CI)
	294/5121	5.7 (5.1, 6.4)	16/94,428	0.02 (0.01, 0.03)
Cytology status*				
Negative	22/2721	0.8 (0.5, 1.2)	2/90,713	0 (0, 0.009)
ASCUS	46/924	5.0 (3.7, 6.6)	1/3150	0.03 (0, 0.2)
ASC-H	35/144	24.3 (17.7, 32.3)	4/87	4.6 (1.5, 12.0)
AGC	14/57	24.6 (14.5, 38.0)	0/268	0 (0, 1.8)
LSIL	34/734	4.6 (3.3, 6.5)	1/147	0.6 (0, 4.3)
HSIL	94/201	46.8 (39.8, 53.9)	5/17	29.4 (11.4, 56.0)
Cancer	8/8	100 (60, 100)	3/3	100 (31, 100)

HPV human papillomavirus, CIN3+ cervical intraepithelial neoplasia 3 or worse, ASCUS atypical squamous cells of undetermined significance, ASC-H atypical squamous cells—cannot exclude high-grade intraepithelial lesion, AGC atypical glandular cells, LSIL low-grade squamous intraepithelial lesion, HSIL high-grade squamous intraepithelial lesion

**375 patients without histological results excluded (no imputed data)*

DISCUSSION

The FDA approval of a primary HPV screening test as an alternative to cytology has introduced complexity into an evolving field and stirred considerable debate over the appropriate screening strategy.[12,25,34] In this retrospective cohort study of 99,549 patients undergoing primary cervical cancer screening in an integrated health system, we found that *Primary HPV* screening was more effective and less expensive than *Primary Cytology. Co-testing* was only slightly more effective than *Primary HPV* testing and was substantially more expensive, costing approximately $170,000 for each additional case of CIN3+ identified.

Three large prospective, population-based studies of cervical cancer screening have been conducted in North America. All reported rates of HPV infection and cervical abnormalities similar to ours.[6,7,16,35–37] In contrast, test characteristics of the strategies varied widely. The sensitivity of HPV testing ranged from 48 to 87 %, and cytology ranged from 51 to 90 %. Specificity varied less, ranging from 92 to 99 % for HPV and 88 % to 99 % for cytology. In our cohort, all testing modalities had high sensitivity (>90 %) and specificity (>97 %). In contrast, the ATHENA study and Canadian Cervical Cancer Screening Trial reported sensitivities below 60 % for all modalities, because their rates of abnormal cytology (which was necessary for advancing to colposcopy in any strategy) were much lower than ours. It is unclear whether this difference was due to sample collection or pathological interpretation.

The superior cost-effectiveness of cervical cancer screening strategies involving HPV testing over cytology alone has been reported in a variety of settings.[38–44] Although *Co-testing* is preferred over *Primary Cytology* by some guidelines,[5] this recommendation has been questioned.[12] Our analysis supports a *Primary HPV* strategy over *Primary Cytology*, because it detected more cases of CIN3+ at lower cost. The higher specificity of *Primary HPV* meant almost 20 % fewer unnecessary colposcopies—a savings of $1.3 million over the study period. Compared to *Co-testing, Primary HPV* avoided most Pap smears and many colposcopies. Because both strategies included HPV testing, the analysis was relatively insensitive to the cost of HPV testing.

To our knowledge, no studies have directly compared 3-year *Primary HPV* and *Co-testing* strategies, and none have

Table 3 Test Characteristics of Three Screening Strategies for Detecting CIN3+

	Primary cytology*,†	Co-testing*,†	Primary HPV*,†
Sensitivity (%, 95 % CI)	90.7 (86.4, 93.8) 244/269	99.3 (97.1, 99.9)§ 267/269	94.1 (90.3, 96.5) 253/269
Specificity (%, 95 % CI)	97.6 (97.5, 97.7) 96,559/98,905	97.6 (97.5, 97.7) 96,559/98,905	98.1 (98.1, 98.2)‖ 97,068/98,905
PPV (%, 95 % CI)‡	9.6 (8.4, 10.8)¶ 285/2965	10.3 (9.1, 11.5)¶ 308/2988	12.1 (10.7, 13.6)¶ 294/2422
NPV (%, 95 % CI)‡	99.97 (99.96, 99.98) 96,559/96,584	100 (99.99, 100)§ 96,559/96,561	99.98 (99.97, 99.99) 97,111/97,127

HPV human papillomavirus, CIN3+ cervical intraepithelial neoplasia 3 or worse
**We assume that the tests conducted after year 1 are perfect in the sense that all test positives are true CIN3+ cases, and all negatives are true negatives*
†Numerators and denominators rounded to nearest integers
‡Includes imputed data for patients with missing colposcopy results
§$p < 0.001$ vs. Primary Cytology and Primary HPV, other comparisons not significant
‖$p < 0.001$ vs. Primary Cytology and Co-testing, other comparisons not significant
¶$p < 0.001$ for all comparisons

included US populations. Several studies utilized mathematical models to simulate the natural history of cervical cancer and evaluate the cost-effectiveness of screening strategies. One Canadian study compared a primary HPV strategy with a 3-year screening interval and a co-testing strategy to cytology alone.[38] However, they did not directly compare these strategies to each other, and an incremental cost-effectiveness could not be ascertained. Another Canadian study found that compared to primary HPV, bi-annual co-testing beginning at age 18 had an incremental cost-effectiveness ratio of >$400,000 per life year gained.[45] Similar findings have been demonstrated in Europe.[46–49] Because our findings cannot be translated into life years saved, the incremental cost-effectiveness of co-testing may be difficult to interpret. What is a reasonable cost for the health care system to bear to detect one additional case of CIN3+? Specifically, is the detection of 14 cases per 100,000 women screened worth $170,096 per case detected, in addition to the inconvenience of an additional 100,277 cytology tests and 566 colposcopies?

Our cohort represents a low-risk population, as evidenced by the lower incidence of LSIL (0.88 %) and HSIL (0.22) than the national median (2.5 % and 0.5 %, respectively).[50] Our study is instructive for other integrated health systems seeking to provide high-value care to similar populations. Given the low rates of disease, the redundancy of co-testing appears to be unnecessary. This conclusion cannot be generalized to high-risk centers, where patients struggle with access to care, and where most cases of cervical cancer occur. In that context, the emphasis must be on consistent screening and assuring timely follow-up.

Our study has several other important limitations. First, for women who did not receive follow-up care, we used imputation to assign outcomes, which may not accurately represent the incidence of CIN3+. The population with imputed results was small, but differed in race, smoking status and insurance from those who underwent colposcopy. Imputation was used only for determining the positive and negative predictive value, so it had no impact on other test characteristics or the cost-effectiveness calculations. Second, without being able to determine the histological status of patients with both negative HPV and cytology tests, our study is susceptible to verification bias; however, other studies have demonstrated negligible incidence of CIN2+ and CIN3+ in the setting of negative co-testing results.[6,51,52] We used only a single co-test, while the importance of assessing screening over at least two rounds has been suggested.[53] Additionally, because all tests were conducted in a high-functioning health care system, test sensitivity may be superior to other settings. Finally, because we used surrogate outcomes, we could not estimate the cost per case of cervical cancer prevented or life years saved.

Our cost-effectiveness analysis is limited to a 3-year screening interval. Because of the difference in screening intervals (3 years for *Primary Cytology* and 5 years for *Primary HPV* and *Co-testing*), we had to estimate the cost of a 3-year interval for the HPV-based strategies in order to compare like outcomes. The cost of storing specimens was considered only in sensitivity analysis. Including such costs would improve the cost-effectiveness of *Co-testing*. It is also important to note that we used current National Medicare Facility Prices. While the prices paid by private insurance may be higher, our marginal costs of *Co-Testing* over *Primary HPV* were relatively insensitive to the cost of HPV testing. Higher cytology prices would make *Co-Testing* less favorable. Our analysis was

Table 4 Number of Tests and Cost by Strategy for Detecting CIN3+ ($N = 99,549$)

	#HPV	#Cytology	#Colposcopy	3-Year total cost*	CIN3+ cases	ΔCost	ΔCases	Marginal cost/Case
Primary cytology	6359	101,649	2966	$4,795,900	285			
Primary HPV	102,270	7842	2422	$3,472,320	294	−$1,323,580	9	−$147,064
Co-testing	108,119	108,119	2988	$5,853,660	308	$2,381,340	14	$170,096

HPV human papillomavirus, CIN3+ cervical intraepithelial neoplasia 3 or worse
**Total cost of Primary HPV and Co-testing strategies multiplied by 3/5 to compare cost of 3-year screening interval for all strategies*

conducted from the payer perspective. Patients, depending on their co-pays and financial means, might feel differently about which strategy they prefer. Finally, we excluded patients who had equivocal HPV results. Including the cost of these tests would not affect the outcome because the number would be the same for both strategies.

The cobas® HPV Test was recently approved for primary cervical cancer screening based on the ATHENA trial.[21,54] Like the Hybrid Capture 2 used in this study, the cobas® Test detects 14 high-risk HPV genotypes. However, the cobas® Test also detects genotype 66 and indicates specifically whether the specimen is positive or negative for HPV-16 or HPV-18.[55] The strong association of cervical cancer with these two genotypes is the basis for a primary HPV screening strategy in which women who test positive for HPV-16/HPV-18+ genotypes are triaged directly for colposcopy. In ATHENA, genotyping for HPV-16/HPV-18 improved the sensitivity for CIN3+ and required far fewer cytology tests with only a marginal increase in colposcopies over co-testing.[35] This should make Primary HPV testing even more cost-effective. However, because of the differences between these tests, our *Primary HPV* strategy is not directly comparable to screening with cobas®.

The findings from this large cohort of women in routine care shed light upon the changing landscape of cervical cancer screening. Primary HPV testing appears to offer an attractive tradeoff between cost and effectiveness. Additional factors may be taken into consideration when selecting the appropriate screening strategy for individual patients, but as value-based care becomes increasingly important, cost and convenience will contribute more to decision making. Overall, the findings from this study provide support for the implementation of primary HPV screening with reflex cytology as a potentially cost-effective strategy in low-risk women age 30 and older.

Author Contributions: *Dr. Jin and Sarah Schramm had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.*
Study concept and design: Jin, Sikon, Lipold, Belinson
Acquisition of data: Schramm, Nottingham, Brainard
Analysis and interpretation of data: Hu, Jin, Lipold, Sikon, Rothberg, Foucher
Drafting of the manuscript: Jin, Foucher, Rothberg, Sikon, Lipold
Critical revision of the manuscript for important intellectual content: All authors
Statistical analysis: Hu
Administrative, technical, or material support: Schramm, Nottingham
Study supervision: Schramm, Nottingham, Jin, Sikon, Lipold

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Corresponding Author: *Xian Wen Jin, MD, PhD; Department of Internal MedicineCleveland Clinic, Cleveland, OH, USA (e-mail: jinx@ccf.org).*

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