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Estimated Quality of Life and Economic Outcomes Associated With 12 Cervical Cancer Screening Strategies
A Cost-effectiveness Analysis

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IMPORTANCE Many cervical cancer screening strategies are now recommended in the United States, but the benefits, harms, and costs of each option are unclear.

OBJECTIVE To estimate the cost-effectiveness of 12 cervical cancer screening strategies.

DESIGN, SETTING, AND PARTICIPANTS The cross-sectional portion of this study enrolled a convenience sample of 451 English-speaking or Spanish-speaking women aged 21 to 65 years from September 22, 2014, to June 16, 2016, identified at women's health clinics in San Francisco. In this group, utilities (preferences) were measured for 23 cervical cancer screening–associated health states and were applied to a decision model of type-specific high-risk human papillomavirus (hrHPV)–induced cervical carcinogenesis. Test accuracy estimates were abstracted from systematic reviews. The evaluated strategies were cytologic testing every 3 years for women aged 21 to 65 years with either repeat cytologic testing in 1 year or immediate hrHPV triage for atypical squamous cells of undetermined significance (ASC-US), cytologic testing every 3 years for women age 21 to 29 years followed by cytologic testing plus hrHPV testing (cotesting), or primary hrHPV testing alone for women aged 30 to 65 years. Screening frequency, abnormal test result management, and the age to switch from cytologic testing to hrHPV testing (25 or 30 years) were varied. Analyses were conducted from both the societal and health care sector perspectives.

MAIN OUTCOMES AND MEASURES Utilities for 23 cervical cancer screening–associated health states (cross-sectional study) and quality-adjusted life-years (QALYs) and total costs for each strategy.

RESULTS Utilities were measured in a sociodemographically diverse group of 451 women (mean [SD] age, 38.2 [10.7] years; 258 nonwhite [57.2%]). Cytologic testing every 3 years with repeat cytologic testing for ASC-US yielded the most lifetime QALYs and conferred more QALYs at higher costs ($2166 per QALY) than the lowest-cost strategy (cytologic testing every 3 years with hrHPV triage of ASC-US). All cytologic testing plus hrHPV testing (cotesting) and primary hrHPV testing strategies provided fewer QALYs at higher costs. Adding indirect costs did not change the conclusions. In sensitivity analyses, hrHPV testing every 5 years with genotyping triage beginning at age 30 years was the lowest-cost strategy when hrHPV test sensitivity was markedly higher than cytologic test sensitivity or when hrHPV test cost was equated to the lowest reported cytologic test cost ($14).

CONCLUSIONS AND RELEVANCE Cytologic testing every 3 years for women aged 21 to 29 years with either continued cytologic testing every 3 years or switching to a low-cost hrHPV test every 5 years confers a reasonable balance of benefits, harms, and costs. Comparative modeling is needed to confirm the association of these novel utilities with cost-effectiveness.

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An estimated 13 240 women in the United States received a diagnosis of cervical cancer in 2018, and 4170 died from the disease.[1] Although large declines in cervical cancer incidence and mortality in the United States have accompanied widespread screening with cervical cytologic testing, screening options have greatly expanded beyond cytologic testing alone. In 2012, major guideline groups in the United States endorsed 4 cervical cancer screening strategies for women aged 21 to 65 years: cervical cytologic testing every 3 years with 2 options for managing atypical squamous cells of undetermined significance (ASC-US), and cervical cytologic testing every 3 years for women aged 21 to 29 years followed by cytologic testing plus testing for high-risk human papillomavirus (hrHPV) every 5 years for women aged 30 to 65 years with 2 options for managing those with normal cytologic test results and positive results of hrHPV testing.[2-4]

In 2014, the US Food and Drug Administration approved a hrHPV test for primary cervical cancer screening in women aged 25 years or older. The American College of Obstetricians and Gynecologists stated that this strategy could be considered as an alternative to current cytologic test-based screening methods[5] and recommended that interim guidance published by the Society of Gynecologic Oncology be followed regarding its use; these guidelines recommended that screening begin at age 25 years, that rescreening occur "no sooner than every 3 years"[6(p334)] and that women with positive results of hrHPV tests be managed based on HPV genotyping results and, in some cases, cytologic test results.

In August 2018, the US Preventive Services Task Force endorsed primary hrHPV testing alone performed at 5-year intervals beginning at age 30 years as a preferred screening strategy[7] along with cytologic testing at 3-year intervals for women aged 21 to 65 years. The group continued to recommend cotesting (cytologic testing plus hrHPV testing) for women aged 30 to 65 years as an alternative strategy.

With various possible test combinations, screening frequencies, and ages to switch from one screening strategy to another, many different cervical cancer screening strategies are now being recommended in the United States. To help identify which strategies might constitute high-value care, some groups have recommended that cost-effectiveness analyses be performed.[2] Prior analyses have been hampered by the lack of a comprehensive, population-derived set of process utilities (preferences) that capture important quality of life outcomes anticipated throughout the contemporary screening process.[8,9] In an effort to contribute to policy discussions regarding high-value cervical cancer screening, we estimated quality of life and economic outcomes associated with 12 strategies by measuring women's preferences and incorporating them into a cost-effectiveness analysis.

Key Points

Question After incorporating women's preferences into a cost-effectiveness analysis, what are the estimated quality of life and economic outcomes associated with cervical cancer screening strategies currently recommended in the United States?

Findings Of 12 strategies evaluated in a cost-effectiveness model, cytologic testing every 3 years for women aged 21 to 29 years with either continued triennial cytologic testing or switching to a low-cost high-risk human papillomavirus test every 5 years from age 30 to 65 years conferred a reasonable balance of benefits, harms, and costs from both a societal and health care sector perspective.

Meaning Cytologic testing every 3 years and low-cost high-risk human papillomavirus testing every 5 years both may be considered reasonable cervical cancer screening options for women aged 30 to 65 years.

Methods

Utility Measurement

We conducted 4 focus groups to aid in constructing scenarios for health states associated with cervical cancer screening (eTable 1 in the Supplement). A sociodemographically diverse group of English-speaking or Spanish-speaking women aged 21 to 65 years was then recruited from 2 women's health clinics in San Francisco, California, between September 22, 2014, and June 16, 2016. The sociodemographic and clinical characteristics of the sample are in eTable 2 in the Supplement. These women were enrolled in a cross-sectional study consisting of a 50-minute, face-to-face interview during which they completed an interviewer-administered questionnaire and viewed a 7-minute educational video. Using a computerized tool, preferences were elicited from participants using the time tradeoff method[10,11] and were used to generate utilities for 23 health states. To prevent fatigue, health states were grouped into 3 sets of 7 or 8; each participant was randomly assigned by computer to assess 2 of the 3 sets. To minimize possible effects of the order in which scenarios were presented, we also randomized the set presentation order. Prior to viewing the educational materials and performing the preference elicitation exercise, the first 262 participants were asked to select a preferred screening strategy; after the exercise was completed, they were again asked to select a preferred strategy (eTable 3 in the Supplement). The University of California, San Francisco and Zuckerberg San Francisco General Hospital Institutional Review Boards approved this study, and written informed consent was obtained from the participants. Details are in eAppendices 1, 2, and 3 in the Supplement.

Model Overview, Inputs, and Assumptions

We constructed an HPV type-specific Markov decision model using data on the natural history of HPV and cervical neoplasia. The model was constructed using TreeAge Pro 2017 (TreeAge Software Inc), and R, version 3.5.0 (R Foundation for Statistical Computing).[12] The natural history model simulated a birth cohort of women at average risk of developing cervical cancer (not immune-compromised and not vaccinated against HPV). In the model, the transition probabilities between health states were HPV type-specific (eFigure 1 in the Supplement). To fully capture changes in health states associated with screening, we used a 1-year Markov cycle length.

The cohort started at age 10 years with no existing HPV infections and was followed over a lifetime (until death or age

100 years). Every year, women were at risk of becoming infected with HPV 16 or 18 or other hrHPV types (eTable 4 in the Supplement). Women could clear their infections, stay infected, or progress to cervical intraepithelial neoplasia, a precancerous lesion. Cervical intraepithelial neoplasia could regress, persist, or progress to higher grades or cancer. Cervical intraepithelial neoplasia grade 1 was included as a health state because current management guidelines endorse treatment if these lesions persist.[13] Women with cancer could have their cancer detected by symptoms as the stage progressed and were at risk of cancer death (eTable 5 in the Supplement). Women were also at risk of age-specific causes of death and of undergoing hysterectomy for noncancerous conditions.

We used Bayesian calibration methods to estimate the parameters of the natural history by matching model-predicted outcomes with calibration targets (eFigures 2-4 in the Supplement). Validation was by comparison with 2 sources: outcomes from a recent randomized trial of hrHPV testing compared with cytologic testing[14] and Surveillance, Epidemiology, and End Results (SEER) data[15] (eFigures 5-7 in the Supplement). Details are in eAppendices 4, 5, and 6 and eTable 6 in the Supplement.

Screening Strategies and Test Accuracy Estimates

We evaluated 12 strategies: cytologic testing every 3 years for women aged 21 to 65 years with either repeat cytologic testing in 1 year or immediate hrHPV triage for women with ASC-US; cytologic testing every 3 years for women aged 21 to 29 years followed by cotesting for women aged 30 to 65 years with either repeat cotesting in 1 year or immediate genotyping triage for women with normal cytologic test results and positive hrHPV test results; cytologic testing every 3 years for women aged 21 to 29 years followed by primary hrHPV testing alone every 3 years or every 5 years for women aged 30 to 65 years with either immediate cytologic testing triage for women with positive hrHPV test results or immediate genotyping triage for women with positive hrHPV test results with additional cytologic testing triage of women with positive hrHPV test results and negative genotyping results. In strategies switching from cytologic testing to hrHPV testing, we also evaluated switching at aged 25 years instead of 30 years (eAppendix 7 and eTable 7 in the Supplement).

For all cotesting and primary hrHPV testing strategies, women underwent cytologic screening prior to beginning hrHPV testing. We included annual cytologic testing as an additional comparator because it is a screening strategy still preferred by many US women.[16,17] Management of abnormal test results and cervical intraepithelial neoplasia treatment were programmed in the model to reflect the complexity of current American Society of Colposcopy and Cervical Pathology guidelines[13] (eTables 7 and 8, eAppendix 8, and eFigures 8-14 in the Supplement). We assumed that all women adhered with screening, follow-up and treatment.

In primary analyses, estimates of screening test accuracy (sensitivity and specificity) were abstracted from recent systematic reviews, including a 2017 Cochrane review (**Table 1**).[18-25] We used cervical intraepithelial neoplasia grade 2 as defining disease because treatment is recommended for most women in the United States with this lesion.[13] In sensitivity analyses, we used accuracy estimates from a multicentered, United States–based study that enrolled more than 47 000 women (the Addressing the Need for Advanced HPV Diagnostics study [ATHENA])[26]; we used unadjusted accuracy estimates and those adjusted for verification bias. We used separate summary accuracy estimates for tests applied in surveillance[21,22] and posttreatment follow-up.[23] Clinical algorithms and utility maps are in eFigures 8-14 in the Supplement.

Costs

We incorporated direct medical costs into our model, reported in 2016 US dollars and accounting for medical inflation. Direct costs associated with screening, diagnosis, and treatment were based on Medicare reimbursement rates (Table 1).[18-25] Costs for cancer, including cancer death, were based on SEER-Medicare claims data.[25] In sensitivity analyses, we included indirect nonmedical costs, including time for patient travel, waiting, and examination.[27] In the absence of published studies on the indirect costs for cervical cancer, we used costs for uterine cancer.[28]

Analysis

The primary outcomes were lifetime costs in 2016 US dollars and quality-adjusted life-years (QALYs) for each strategy, both discounted at an annual rate of 3%. Each utility was mapped to an outcome for a specific strategy that would occur during a 1-year period (eFigures 8-14 in the Supplement); only 1 utility per unique outcome was applied. As recommended,[29] cost-effectiveness analyses were conducted from both a societal and health care sector perspective. Incremental cost-effectiveness ratios were calculated by dividing the additional cost by the additional health benefit of a specific strategy compared with the next less costly, nondominated strategy.

Sensitivity Analyses: Deterministic

We performed deterministic sensitivity analyses to examine the independent effect of the following on total costs, QALYs, and incremental cost-effectiveness ratios: adding indirect costs, substituting ATHENA test accuracy estimates, and equating hrHPV test cost with the reported lower bound for the cost of a cytologic test ($14). We explored the result of substituting accuracy estimates in the primary screening setting with the highest summary specificity estimates reported for hrHPV testing (Table 1)[18-25]; because of a lack of direct evidence regarding how this change in specificity affects accuracy estimates for cotesting and primary hrHPV testing with genotyping triage, these strategies were excluded from this model. To explore the independent effect of utilities on our results, we removed utilities stepwise by the categories defined in Table 1[18-25] (screening, then surveillance, then false-positive testing, then treatment and cancers).

Sensitivity Analyses: Probabilistic

To account for model input parameter uncertainty, we randomly sampled values from parameter distributions. For the calibrated parameters, we sampled from the posterior distribution

Table 1. Model Inputs for Utilities, Test Accuracy Estimates, and Costs

Variable	Value	Source
Screening results, utility, mean (95% CI)[a]		
Normal cytologic test	0.97294 (0.96343-0.98103)	Current study
Normal cytologic test in past; no testing this year	0.97643 (0.96818-0.98338)	Current study
Normal cytologic test, negative hrHPV test	0.97061 (0.96224-0.97819)	Current study
Normal cytologic test, negative hrHPV test in past; no testing this year	0.96465 (0.95281-0.97444)	Current study
Negative hrHPV test	0.96017 (0.94648-0.97146)	Current study
Negative hrHPV test in past; no testing this year	0.96096 (0.94673-0.97299)	Current study
ASC-US cytologic test, negative hrHPV test in past; no testing this year	0.94564 (0.93220-0.95896)	Current study
Simple hysterectomy in the past; no testing this year	0.86506 (0.83926-0.88782)	Current study
Surveillance, mean (95% CI)[a]		
ASC-US cytologic test; repeat cytology in 1 y	0.94740 (0.93410-0.95937)	Current study
ASC-US cytologic test, negative hrHPV test	0.94405 (0.93116-0.95633)	Current study
Normal cytologic test, positive hrHPV test; repeat both in 1 y	0.93408 (0.91845-0.94873)	Current study
CIN2, no treatment; repeat colposcopy	0.91417 (0.89429-0.93204)	Current study
False-positive test results, mean (95% CI)[a]		
Abnormal cytologic test, normal colposcopy	0.96108 (0.94932-0.97167)	Current study
Abnormal cytologic test, positive hrHPV test, normal colposcopy	0.94492 (0.93062-0.95815)	Current study
Positive hrHPV test, normal colposcopy	0.94238 (0.92658-0.95825)	Current study
Normal cytologic test, persistently positive hrHPV test, normal colposcopy	0.93713 (0.92110-0.95177)	Current study
Treatment, mean (95% CI)[a]		
Ablative therapy	0.94993 (0.93626-0.96174)	Current study
Excisional therapy	0.91356 (0.89322-0.93178)	Current study
Simple hysterectomy	0.83865 (0.81238-0.86427)	Current study
Early-stage cervical cancer, radical hysterectomy	0.78385 (0.74342-0.82457)	Current study
Early-stage cervical cancer, radical hysterectomy in past; no testing this year	0.77935 (0.73675-0.81643)	Current study
Advanced-stage cervical cancer, radiotherapy and chemotherapy	0.72767 (0.68368-0.77222)	Current study
Advanced-stage cervical cancer, radiotherapy and chemotherapy in past; no testing this year	0.73586 (0.68869-0.78337)	Current study
Test Accuracy Estimates		
Screening setting, primary estimates, sensitivity/specificity[a]		
Cytologic testing	0.755 (range, 0.43-0.96)/ 0.919 (range, 0.73-0.98)	Koliopoulos et al,[18] 2017
hrHPV testing	0.926 (range, 0.61-1.00)/ 0.893 (range, 0.58-0.97)	Koliopoulos et al,[18] 2017
Cytologic testing plus hrHPV testing (cotesting)	0.937 (range, 0.75-1.00)/ 0.858 (range, 0.32-0.93)	Li et al,[19] 2016
Screening setting, secondary estimates (ATHENA, adjusted for verification bias), sensitivity/specificity		
Cytologic testing	0.353/0.941	FDA,[20] 2014
hrHPV testing	0.613/0.905	FDA,[20] 2014
Cytologic testing plus hrHPV testing (cotesting)	0.649/0.868	FDA,[20] 2014
Screening setting, secondary estimates (ATHENA, unadjusted), sensitivity/specificity[b]		
Cytologic testing	0.552/0.950	FDA,[20] 2014
hrHPV testing	0.945/0.921	FDA,[20] 2014
Cytologic testing plus hrHPV testing (cotesting)	1.0/0.890	FDA,[20] 2014
Screening setting, high-specificity estimate for hrHPV testing	0.927/0.933	Koliopoulos et al,[18] 2017
Surveillance setting, sensitivity/specificity		
Cytologic testing	0.818/0.576	Arbyn et al,[21] 2004
Cytologic testing plus hrHPV testing (cotesting)	0.997/0.413	Arbyn et al,[22] 2015

(continued)

Table 1. Model Inputs for Utilities, Test Accuracy Estimates, and Costs (continued)

Variable	Value	Source
Posttreatment follow-up setting, sensitivity/specificity		
Cytologic testing	0.79/0.81	Kocken et al,[23] 2012
Cytologic testing plus hrHPV testing (cotesting)	0.95/0.67	Kocken et al,[23] 2012
Service, Test, and Treatment, Cost (Range), $[a]		
Office visit	73 (47-92)	CMS[24]
Cytologic testing	25 (14-28)	CMS[24]
hrHPV testing	44 (26-47)	CMS[24]
Colposcopy and biopsy	226 (166-284)	CMS[24]
Cryosurgery	145 (120-230)	CMS[24]
Loop excision	524 (387-1636)	CMS[24]
Cold knife cone biopsy	1569 (1449-1701)	CMS[24]
Cancer care, first year		
Age <65 y	64 742 (NA)	Mariotto et al,[25] 2011
Age ≥65 y	53 950 (NA)	Mariotto et al,[25] 2011
Cancer care, ongoing	1702 (NA)	Mariotto et al,[25] 2011
Cancer care, last year of life		
Age <65 y	141 201 (NA)	Mariotto et al,[25] 2011
Age ≥65 y	94 134 (NA)	Mariotto et al,[25] 2011

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; ATHENA, Addressing the Need for Advanced HPV Diagnostics study; CIN2, cervical intraepithelial neoplasia grade 2; CMS, Centers for Medicare & Medicaid Services; FDA, US Food and Drug Administration; hrHPV, high-risk human papillomavirus; NA, not available.

[a] Range used in probabilistic sensitivity analysis.

[b] Restricted to verified cases of CIN2 or worse and assuming women with normal cytologic test results and negative hrHPV test results did not have CIN2 or worse.

obtained from the Bayesian calibration approach (eAppendix 5 in the Supplement). In total, we performed 10 000 iterations of Monte Carlo simulations to evaluate the effect of varying all model inputs simultaneously for each strategy (ranges in Table 1[18-25]) on cost-effectiveness results.

Results

We measured utilities (Table 1) in 451 women. Their mean (SD) age was 38.2 (10.7) years, 258 (57.2%) were nonwhite, and 151 (35.7%) had less than a college degree (eTable 2 in the Supplement). Estimated lifetime screening outcomes per 1000 women demonstrated more false-positive test results associated with hrHPV test-based strategies with concurrent lower cancer incidence (**Table 2**). Cancer mortality ranged from 0.9 to 1.4 per 1000 women who underwent screening compared with 19.0 per 1000 women who did not undergo screening.

Screening was cost-saving compared with no screening ($1267-$2577 per woman vs $2891 per woman). Cytologic testing every 3 years with repeat cytologic testing for ASC-US yielded the most lifetime QALYs (28.91174) (**Table 3**). Cytologic testing every 3 years with hrHPV triage of ASC-US was the lowest-cost strategy ($1267 per woman), and cytologic testing every 3 years with repeat cytologic testing for ASC-US conferred more QALYs at higher costs ($2166 per QALY). Cotesting and primary hrHPV testing provided fewer QALYs at higher costs (ie, were dominated). Annual cytologic testing was the most costly strategy but provided fewer QALYs than did cytologic testing every 3 years (lifetime costs, $2577; QALYs, 28.80491).

Sensitivity Analyses

Adding indirect costs did not change our conclusions about cost-effectiveness (Table 3). When the costs of hrHPV testing were equated to the lower bound of cytologic testing ($14), hrHPV testing every 5 years with genotyping triage for women with positive hrHPV test results and additional cytologic triage of women with positive hrHPV test results and negative genotyping- results beginning at age 30 years was the lowest-cost strategy ($1183). Additional QALYs at higher costs were conferred by cytologic testing every 3 years with hrHPV triage of ASC-US ($708 per QALY) and further with cytologic testing every 3 years with repeat cytologic testing in 1 year for ASC-US ($2590 per QALY).

When we substituted ATHENA test accuracy estimates adjusted for verification bias in which hrHPV test sensitivity was markedly greater than that of cytologic testing (0.649 vs 0.313), hrHPV testing every 5 years with genotyping triage for women with positive hrHPV test results and additional cytologic triage of women with positive hrHPV test results and negative genotyping results beginning at age 30 years was the lowest-cost strategy; additional QALYs at higher costs were conferred by cytologic testing every 3 years with hrHPV triage of ASC-US ($715 per QALY) and further with cytologic testing every 3 years with repeat cytologic testing for ASC-US ($2446 per QALY). Conclusions were similar when we used unadjusted ATHENA accuracy estimates (eAppendix 9 and eTable 9 in the Supplement). When we substituted a high-specificity estimate for hrHPV testing (0.933),[18] hrHPV testing every 5 years with cytologic triage beginning at age 30 years was the least costly strategy ($1230 per woman); additional QALYs at higher costs could be achieved with cytologic testing every 3 years with hrHPV triage of ASC-US ($488 per QALY) and further with cytologic testing every 3 years with repeat cytologic testing in 1 year for ASC-US ($2166 per QALY; eTable 9 in the Supplement).

Although utilities for health states involving hrHPV testing for screening and surveillance were generally lower than those for cytologic testing (Table 1), removal of these utilities

Table 2. Estimated Cervical Cancer Screening Outcomes per 1000 Women Over a Lifetime, by Source of Test Accuracy Estimates

Screening Strategy	Screening, Surveillance, and Treatment Outcomes, No.			Cervical Cancer Outcomes, No.			
	Colposcopies	False-Positive Test Results[a]	Treatments[b]	Stage 1	Stage ≥2	All Stages	Cancer Deaths
No screening	NA	NA	NA	14.38	15.81	30.19	19.02
Primary Analysis: Using Accuracy Estimates From Systematic Reviews and Meta-analyses							
Cytologic testing every 3 y							
Repeat cytologic test in 1 y for ASC-US	1870	1223	440	1.74	0.67	2.41	1.44
hrHPV triage for ASC-US	2074	1429	421	1.58	0.64	2.22	1.30
Cytologic testing and hrHPV test (cotesting) every 5 y							
Repeat in 1 y for normal cytologic test results and positive hrHPV test results	2696	2125	584	1.56	0.63	2.19	1.29
Genotyping triage for normal cytologic test results and positive hrHPV test results	2879	2294	585	1.53	0.62	2.15	1.27
hrHPV testing every 3 y, cytologic triage for positive hrHPV test results							
Begin at age 25 y	2734	2208	603	1.22	0.36	1.58	0.94
Begin at age 30 y	2707	2147	570	1.33	0.38	1.71	1.03
hrHPV testing every 5 y, cytologic triage for positive hrHPV test results							
Begin at age 25 y	2179	1708	517	1.79	0.54	2.33	1.41
Begin at age 30 y	2176	1654	495	1.81	0.55	2.36	1.42
hrHPV testing every 3 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping							
Begin at age 25 y	3090	2508	599	1.19	0.48	1.67	0.097
Begin at age 30 y	3009	2416	568	1.29	0.48	1.77	1.0
hrHPV testing every 5 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping							
Begin at age 25 y	2488	1966	518	1.65	0.55	2.2	1.30
Begin at age 30 y	2425	1874	496	1.69	0.56	2.25	1.34
Secondary Analysis: Using Accuracy Estimates From ATHENA Study, Adjusted for Verification Bias							
Cytologic testing every 3 y							
Repeat cytologic test in 1 y for ASC-US	1364	963	317	3.98	2.33	6.31	3.52
hrHPV triage for ASC-US	1481	1075	295	3.78	2.33	6.11	3.49
Cytologic testing and hrHPV test (cotesting) every 5 y							
Repeat in 1 y for normal cytologic test results and positive hrHPV test results	2282	1911	491	3.14	1.61	4.75	2.56
Genotyping triage for normal cytologic test results and positive hrHPV test results	2481	2083	492	2.92	1.61	4.53	2.51
hrHPV testing every 3 y, cytologic triage for positive hrHPV test results							
Begin at age 25 y	2457	2045	531	2.23	0.88	3.11	1.78
Begin at age 30 y	2379	1983	489	2.64	1.12	3.76	2.09
hrHPV testing every 5 y, cytologic triage for positive hrHPV test results							
Begin at age 25 y	1913	1559	439	3.28	1.60	4.88	2.85
Begin at age 30 y	1854	1498	407	3.55	1.77	5.32	3.08
hrHPV testing every 3 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping							
Begin at age 25 y	2769	2307	528	2.10	0.97	3.07	1.74
Begin at age 30 y	2642	2219	486	2.51	1.16	3.67	2.03
hrHPV testing every 5 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping							
Begin at age 25 y	2177	1780	439	2.97	1.52	4.49	2.58
Begin at age 30 y	2066	1687	408	3.26	1.69	4.95	2.82

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; ATHENA, Addressing the Need for Advanced HPV Diagnostics study; hrHPV, high-risk human papillomavirus; NA, not applicable.

[a] Positive test results that lead to colposcopy in which no cervical intraepithelial neoplasia grade 2 or worse is found.

[b] Cryosurgeries, loop excisions, or cone biopsies.

did not change our conclusions about cost-effectiveness; the incremental cost-effectiveness ratio of cytologic testing every 3 years with repeat cytologic testing in 1 year for ASC-US compared with cytologic testing every 3 years with hrHPV triage of ASC-US increased from $2166 per QALY to $21 795 per QALY. Additionally removing utilities associated with false-positive test results suggested that cytologic testing every 3 years with hrHPV triage of ASC-US dominated all other

Table 3. Estimated Lifetime Costs, QALYs, and ICERs

Screening Strategy	Cost, $	QALYs	ICER, $/QALYs[a]
Primary Analysis: Using Accuracy Estimates From Systematic Reviews and Meta-analyses			
Cytologic testing every 3 y, hrHPV triage for ASC-US	1267	28.84109	0
hrHPV testing every 5 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 30 y	1303	28.76624	Dominated
hrHPV testing every 5 y, cytologic triage for positive hrHPV test results, begin at age 30 y	1311	28.75601	Dominated
hrHPV testing every 5 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 25 y	1355	28.73210	Dominated
hrHPV testing every 5 y, cytologic triage for positive hrHPV test results, begin at age 25 y	1359	28.72099	Dominated
Cytologic testing every 3 y, repeat cytologic testing in 1 y for ASC-US	1420	28.91174	2166
Cytologic and hrHPV testing (cotesting) every 5 y			
Repeat cotesting in 1 y for normal cytologic test results and positive hrHPV test results	1480	28.81260	Dominated
Genotyping triage for normal cytologic test results and positive hrHPV test results	1491	28.81007	Dominated
hrHPV testing every 3 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 30 y	1492	28.73761	Dominated
hrHPV testing every 3 y, cytologic triage for positive hrHPV test results, begin at age 30 y	1507	28.71668	Dominated
hrHPV testing every 3 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 25 y	1589	28.71363	Dominated
hrHPV testing every 3 y, cytologic triage for positive hrHPV test results, begin at age 25 y	1600	28.68792	Dominated
Secondary Analysis: Using Accuracy Estimates From ATHENA Study, Adjusted for Verification Bias			
hrHPV testing every 5 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping			
Begin at age 30 y	1482	28.74043	0
Begin at age 25 y	1503	28.71014	Dominated
hrHPV testing every 5 y, cytologic triage for positive hrHPV test results			
Begin at age 30 y	1515	28.73124	Dominated
Begin at age 25 y	1531	28.69984	Dominated
Cytologic testing every 3 y, hrHPV triage for ASC-US	1537	28.81736	715
hrHPV testing every 3 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 30 y	1591	28.71827	Dominated
hrHPV testing every 3 y, cytologic tests for positive hrHPV test results, begin at age 30 y	1617	28.69958	Dominated
Cytologic and hrHPV testing (cotesting) every 5 y			
Repeat cotesting in 1 y for normal cytologic test results and positive hrHPV test results	1636	28.79016	Dominated
Genotyping for normal cytologic test results and positive hrHPV test results	1642	28.78897	Dominated
hrHPV testing every 3 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 25 y	1645	28.69942	Dominated
hrHPV testing every 3 y, cytologic triage for positive hrHPV test results, begin at age 25 y	1669	28.67583	Dominated
Cytologic testing every 3 y, repeat cytologic testing in 1 y for ASC-US	1717	28.89095	2446
Sensitivity Analysis: Adding in Indirect Costs			
Cytologic testing every 3 y, hrHPV triage for ASC-US	1581	28.84109	0
hrHPV testing every 5 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 30 y	1604	28.76624	Dominated
hrHPV testing every 5 y, cytologic triage for positive hrHPV test results, begin at age 30 y	1612	28.75601	Dominated
hrHPV testing every 5 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 25 y	1666	28.73210	Dominated

(continued)

Table 3. Estimated Lifetime Costs, QALYs, and ICERs (continued)

Screening Strategy	Cost, $	QALYs	ICER, $/QALYs[a]
hrHPV testing every 5 y, cytologic triage for positive hrHPV test results, begin at age 25 y	1668	28.72099	Dominated
Cytologic testing every 3 y, repeat cytologic testing in 1 y for ASC-US	1806	28.91174	3184
Cytologic and hrHPV testing (cotesting) every 5 y			
Repeat cotesting in 1 y for normal cytologic results and positive hrHPV test results	1821	28.81260	Dominated
Genotyping triage for normal cytologic results and positive hrHPV test results	1835	28.81007	Dominated
hrHPV testing every 3 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 30 y	1844	28.73761	Dominated
hrHPV testing every 3 y, cytologic triage for positive hrHPV test results, begin at age 30 y	1861	28.71668	Dominated
hrHPV testing every 3 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 25 y	1963	28.71363	Dominated
hrHPV testing every 3 y, cytologic triage for positive hrHPV test results, begin at age 25 y	1974	28.68792	Dominated
Sensitivity Analysis: Using a Low-Cost hrHPV Test ($14)			
hrHPV testing every 5 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 30 y	1183	28.76624	0
hrHPV testing every 5 y, cytologic triage for positive hrHPV test results, begin at age 30 y	1188	28.75601	Dominated
hrHPV testing every 5 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 25 y	1210	28.73210	Dominated
hrHPV testing every 5 y, cytologic triage for positive hrHPV test results, begin at age 25 y	1211	28.72099	Dominated
Cytologic testing every 3 y, hrHPV triage for ASC-US	1236	28.84109	708
hrHPV testing every 3 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 30 y	1330	28.73761	Dominated
hrHPV testing every 3 y, cytologic triage for positive hrHPV test results, begin at age 30 y	1335	28.71668	Dominated
Cytologic and hrHPV testing (cotesting) every 5 y, repeat cotesting in 1 y for normal cytologic results and positive hrHPV test results	1359	28.81260	Dominated
Cytologic and HPV testing (cotesting) every 5 y, genotyping triage for normal cytologic results and positive hrHPV test results	1370	28.81007	Dominated
hrHPV testing every 3 y, genotyping triage for positive hrHPV test results plus cytologic triage if positive hrHPV test results and negative genotyping, begin at age 25 y	1393	28.71363	Dominated
hrHPV testing every 3 y, cytologic triage for positive hrHPV test results, begin at age 25 y	1393	28.68792	Dominated
Cytologic testing every 3 y, repeat cytologic testing in 1 y for ASC-US	1419	28.91174	2590

Abbreviations: ASC-US, atypical squamous cells of undetermined significance; ATHENA, Addressing the Needs for Advanced HPV Diagnostics study; hrHPV, high-risk human papillomavirus; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years.

[a] Dominated strategies provide fewer QALY at greater costs than the adjacent, nondominated, lower-cost strategy.

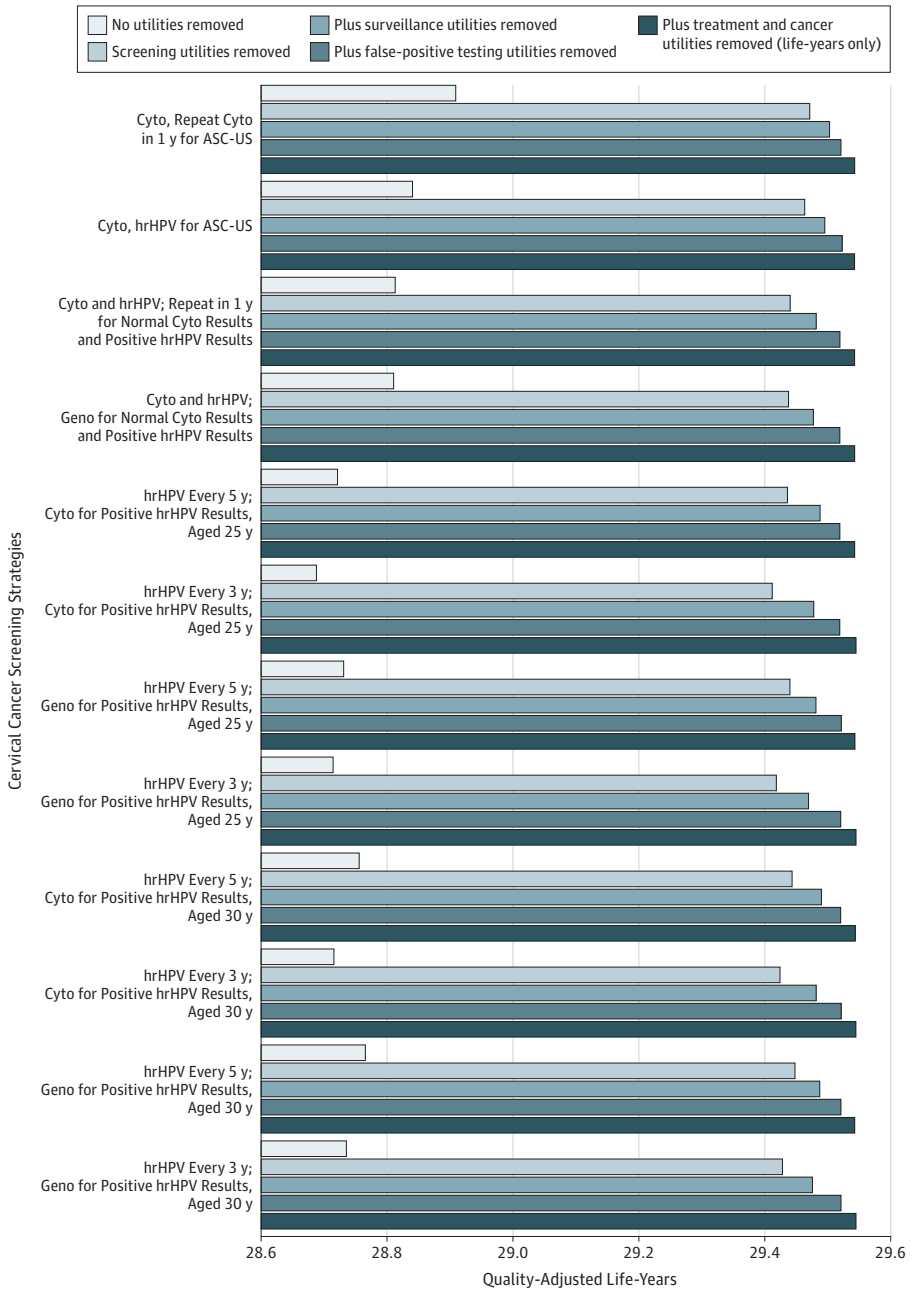
strategies. When all utilities were removed, hrHPV testing every 3 years with genotyping triage for women with positive hrHPV test results and additional cytologic triage of women with positive hrHPV test results and negative genotyping results beginning at age 25 years conferred more life-years than did cytologic testing with hrHPV triage of ASC-US (29.54523 vs 29.54286 life-years; $135 865 per life-year; **Figure 1**).

Probabilistic sensitivity analyses showed that at cost-effectiveness thresholds of $50 000 per QALY, $100 000 per QALY and $150 000 per QALY, cytologic testing every 3 years with repeat cytologic testing for ASC-US was cost-effective in 95% to 96% of iterations (**Figure 2**). Cytologic testing with hrHPV triage of ASC-US every 3 years was cost-effective in 4% to 5% of iterations and primary hrHPV testing every 5 years was cost-effective in 0.01% to 0.04% of iterations. Beginning hrHPV testing prior to age 30 years, performing hrHPV testing every 3 years, and cotesting were cost-effective in 0% of iterations (ie, not cost-effective).

Discussion

Of 12 strategies evaluated, our findings suggest that cytologic testing every 3 years for women aged 21 to 29 years with either continued cytologic testing every 3 years or switching to a low-cost hrHPV test every 5 years from age 30 to 65 years confers a reasonable balance of benefits, harms, and costs from both a societal and health care sector perspective. Cytologic testing plus hrHPV testing (cotesting) did not appear to be cost-effective under any condition we evaluated. Both the American College of Obstetricians and Gynecologists and the American Cancer Society consider cotesting the preferred cervical cancer screening strategy, and the US Preventive Services Task Force considers it an alternative strategy. Our findings challenge these endorsements. Furthermore, our analyses suggest that it is not cost-effective to begin primary hrHPV testing prior to age 30 years, to perform hrHPV testing every 3 years,

Figure 1. Effect of Sequential Utility Removal on Estimated Quality-Adjusted Life-Years Using Accuracy Estimates From Systematic Reviews and Meta-analyses



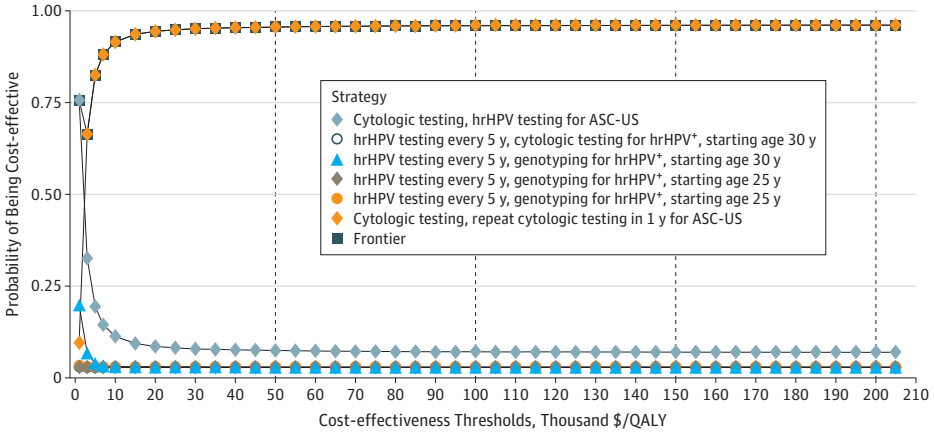
ASC-US indicates atypical squamous cells of undetermined significance; cyto, cytologic testing; geno, genotyping; and hrHPV, high-risk human papillomavirus testing.

or to perform cytologic testing annually. Comparative modeling is needed to confirm these findings.

Our sensitivity analyses identified 3 factors that are potentially associated with the cost-effectiveness of hrHPV testing: test sensitivity, test specificity, and test cost. When we used ATHENA estimates in which hrHPV test sensitivity was markedly greater than that of cytologic testing (0.649 vs 0.313), hrHPV testing every 5 years with genotyping triage for women with positive hrHPV test results and additional cytologic triage of women with positive hrHPV test results and negative genotyping results beginning at age 30 years was the lowest-cost strategy, suggesting that full-cost hrHPV testing may be a reasonable approach to screening in some US settings. The ATHENA estimate for cytologic test sensitivity, however, was lower than all 15 estimates summarized in the 2017 Cochrane review[18] (range, 0.52-0.94); the generalizability of ATHENA findings to other screening settings has been questioned.[30]

Our finding that primary hrHPV testing every 5 years with cytologic triage is the lowest-cost strategy when test specificity is relatively high demonstrates a tangible way in which the screening process might be improved; using tests with a relatively low specificity often leads to surveillance, a costly health

Figure 2. Probability of Each Strategy Being Cost-effective at Various Cost-effectiveness Thresholds



The likelihood of each strategy being cost-effective across all the simulations of the probabilistic sensitivity analysis over a range of cost-effectiveness thresholds. The cost-effectiveness acceptability frontier illustrates the strategy with the highest expected net monetary benefit at each threshold; the net monetary benefit is defined as the difference between the product of quality-adjusted life-years (QALYs) and the cost-effectiveness threshold minus the costs for each of the simulations of the probabilistic sensitivity analyses. The strategy of high-risk human papillomavirus (hrHPV) testing every 5 years with cytologic testing for positive hrHPV test results beginning at age 30 years is not visible because of overlap by the strategy of hrHPV testing every 5 years with cytologic testing for positive hrHPV test results beginning at age 25 years; the 6 strategies not shown had zero probability of being cost-effective at all evaluated thresholds. ASC-US indicates atypical squamous cells of undetermined significance; and hrHPV+, positive test results for hrHPV. The vertical dashed lines indicate cost-effectiveness thresholds.

state to which our participants assigned relatively low utilities. Our high-specificity estimate was derived from a hrHPV test targeting E6 and E7 mRNA.[18] This analysis, however, was limited by our inability to compare primary hrHPV testing with all other 11 strategies. Our sensitivity analysis of hrHPV test costs demonstrated that the attractiveness of hrHPV testing could be improved directly by lowering the cost of the test.

We chose the QALY as our primary outcome because it is a widely recognized measure that combines length of life and population-derived health-related quality of life in a single measure.[31,32] Other recent cost-effectiveness analyses that have found hrHPV test–based strategies to be more favorable to cytologic testing–based strategies in US settings have used outcomes other than the QALY.[33,34] Other analyses have been limited by the use of utilities derived from expert panels.[35,36]

Investigators of a recent randomized clinical trial[37] comparing 2 of the 12 strategies we evaluated (cytologic testing with hrHPV triage of ASC-US vs hrHPV testing with cytologic triage of positive hrHPV tests) stated that the cost-effectiveness of these strategies would need to be understood. Our cost-effectiveness analysis suggests that over a lifetime of screening, cytologic testing every 3 years with hrHPV triage of ASC-US dominates hrHPV testing with cytologic triage of positive hrHPV tests performed either every 3 years or every 5 years (Table 3).

Limitations and Strengths

Our study has important limitations. Although our participants were recruited from 2 clinical settings, the preferences we measured may not be generalizable to other populations. We did not identify any demographic or clinical characteristic by which the utilities varied; these analyses, however, may have been underpowered to detect differences (eTables 10 and 11 in the Supplement). Despite providing participants with clinical information in visual, written, and audio formats along with a research assistant to provide clarifications, we could not be assured that participants understood the information or its relevance to the time tradeoff exercise. Our estimates of incident cancers are higher than those reported recently,[38] as were our estimates of cancer deaths, perhaps because of differential assumptions regarding natural history. Other differences may be because of the intensity with which we modeled guideline-recommended surveillance and posttreatment follow-up. We did not consider the projected effect of HPV vaccination because of limited evidence concerning screening outcomes among vaccinated women as well as current recommendations by all major guideline groups that vaccinated women be screened no differently than unvaccinated women. To allow comparisons with outcomes from other studies, we assumed 100% adherence. How adherence at the numerous steps in the screening process may differ by strategy is uncertain, but may affect screening effectiveness. Finally, we used age-specific transitions to model natural history in contrast with time-in-state dependent transitions,[38] highlighting the need to confirm our findings using comparative modeling.

Our study also has strengths. Our measurement of a comprehensive set of health process utilities specific to cervical cancer screening in a sociodemographically diverse group of women allowed comparisons of quality of life outcomes conferred by each and demonstration of the independent effect of utilities on cost-effectiveness results. By using accuracy estimates drawn from enrollees in a single large US study, we provided more direct comparisons of all strategies in sensitivity analyses. We also followed detailed contemporary clinical algorithms and adjusted both sensitivity and specificity in the surveillance and posttreatment settings to more accurately

reflect the benefits, harms, and costs incurred throughout the full trajectory of recommended care in the United States.

Conclusions

Without quality adjustments, conferred life-years varied little among all 12 screening strategies (29.54175-29.54523 life-years; Figure 1), a finding that underscores the importance of quantifying screening harms and costs unique to each strategy. Identifying and promoting strategies that maximize quality of life outcomes and minimize costs at all steps throughout the screening process will provide higher-value cervical cancer screening from the perspectives of society, the health care sector, and women.

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