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Cost-Effectiveness of 21 Alternative Cervical Cancer Screening Strategies

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ABSTRACT

Objectives: The aim of this study is to assess the cost-effectiveness of 21 alternative cervical cancer screening (CCS) strategies.

Methods: A cohort simulation model was developed to determine from a health systems perspective the cost-effectiveness of the 21 alternative CCS strategies that incorporated combinations of Papanicolaou's smear test (PAP), liquid-based cytology (LBC) or human papillomavirus deoxyribonucleic acid (HPV-DNA) testing. The model was calibrated to categorize total costs into four budgetary authorities: testing, physician, inpatient, and outpatient services. Within each category, alternative screening strategies were contrasted in terms of their cost impacts and the percent change calculated within each category. Epidemiologic data and costs were derived from administrative health databases. Estimates of test characteristics and quality-adjusted life years (QALYs) were derived from available literature.

Results: Three-year screening with PAP and HPV-DNA triage testing for women older than 30 years of age (3-year PAP + HPV + PAP-age) is less costly and more effective saving $16,078 per additional QALY gained. Although there was an associated net cost decrease of 4.2% driven by a reduction in testing and physician costs of 22.1% and 18.6%, respectively, there is a cost increase of 0.8% and 27.7% in inpatient and outpatient services, respectively.

Conclusion: There is economic evidence to support adopting 3-year PAP + HPV + PAP-age. Budgetary resources can potentially be shifted from testing and physician services to fund the additional resource requirements for inpatient and outpatient services.

Keywords: cancer, cost-effectiveness analysis, economic evaluation, Markov model.

Introduction

Cervical cancer (CC) is considered a largely preventable disease through the detection, treatment, and follow-up of its precursors such as human papillomavirus (HPV) and cervical intraepithelial neoplasia (CIN) (i.e., precancerous lesions on the cervix) [1–3]. Conventional cervical cytology (Papanicolaou's smear test—PAP) has been used for more than 50 years to detect CC and its precursors in industrialized countries [4]. Newer assays have been developed that include liquid-based cytology (LBC) and HPV deoxyribonucleic acid (DNA) testing (HPV-DNA). Compared to PAP, LBC is more sensitive and provides greater consistency in the quality of the tissue sample used for cytological analysis [3]. Alternatively, HPV-DNA is a molecular assay that can be used to detect the presence of high-risk oncogenetic strains of HPV (only high-risk oncogenetic HPV strains potentially lead to CC).

Both the LBC and HPV-DNA assays offer promise in providing more effective CC screening algorithms but both are associated with a higher cost per test. The objective was to conduct an economic evaluation to determine the cost-effectiveness of alternative CC screening strategies employing LBC and/or HPV-DNA.

Methods

Screening Alternatives

There were seven alternative screening and testing algorithms (contact the author for flow diagrams). Each alternative was evaluated at 1-, 2-, and 3-year screening intervals giving a total of 21 alternatives.

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PAP + PAP (current). Women aged 18 to 69 are routinely screened annually with PAP. There are seven potential cytological results from a PAP test (presented in order of increasing severity): unsatisfactory specimen (i.e., specimen is insufficient for analysis); negative; atypical squamous cells of undetermined significance (ASCUS); low-grade squamous intraepithelial lesion (LSIL); atypical squamous cells, cannot exclude (ASCH); atypical glandular cells (AGC); and high-grade squamous intraepithelial lesion (HSIL). Women with unsatisfactory specimens are requested to have a repeat PAP test every 3 months until a satisfactory specimen is obtained while women with negative results return to routine screening.

Women with ASCH, AGC, or HSIL are immediately referred for colposcopy and biopsy for histologic assessment of the cervix. Based on the histologic assessment, women with CIN (i.e., lesions) graded as CIN1 or less receive another colposcopy/biopsy in 6 months and if the results are again graded as CIN1 or less they return to routine screening. Women with CIN graded greater than CIN1 (i.e., CIN2 or CIN3) have the CIN removed by a conization procedure and receive a hysterectomy.

Women with ASCUS or LSIL are retested with PAP in 6 months. Women with an unsatisfactory specimen are requested to have a repeat PAP test every 3 months until a satisfactory specimen is obtained. Women with ASCUS or greater are immediately referred for colposcopy and biopsy and follow the histologic assessment described above. Women with negative results are retested with PAP in 6 months and the follow-up process is repeated three times (total of 2 years of follow-up). Women who repeatedly test negative at the end of their 2-year follow-up return to routine screening.

PAP + HPV + PAP. The screening and testing protocol is identical to that of PAP + PAP with one exception. Women with ASCUS are contacted to have an HPV-DNA as a triage test for the presence of high-risk oncogenetic HPV (note that women return to the clinic). Women with negative results for high-risk

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HPV return to routine screening while women with positive results are immediately referred for colposcopy and biopsy.

PAP + HPV + PAP-age (age restriction). The screening and testing protocol is identical to that of PAP + HPV + PAP with one exception. Only women 30 years of age or older who have ASCUS receive a HPV-DNA triage test.

LBC + HPV + LBC. The screening and testing protocol is identical to that of PAP + HPV + PAP with two exceptions. First, routine screening is conducted with LBC. Second, women with LSIL are retested with LBC in 6 months instead of PAP.

LBC + HPV + LBC-age (age restriction). The screening and testing protocol is identical to that of LBC + HPV + LBC with one exception. Only women 30 years of age or older who have ASCUS receive a HPV-DNA triage test.

HPV + LBC + HPV/LBC. Women aged 18 to 69 are routinely screened with HPV-DNA. Women who test negative for high-risk oncogenetic HPV return to routine screening conducted every 3 years while women who test positive for high-risk oncogenetic HPV receive an LBC triage test. Women with an unsatisfactory specimen are requested to have a repeat LBC test every 3 months until a satisfactory specimen is obtained. Women with negative results return to routine screening. Women with ASCH, AGC, or HSIL are immediately referred for colposcopy and biopsy for histologic assessment of their cervix identical to that described for PAP + PAP.

Women with ASCUS or LSIL are retested with both LBC and HPV-DNA in 6 months. Women who test negative for high-risk oncogenetic HPV and who have a negative, unsatisfactory ASCUS or LSIL result on LBC return to routine screening conducting every 3 years. Women who test positive for high-risk oncogenetic HPV and who have ASCH, AGC, or HSIL on LBC are immediately referred to colposcopy and biopsy for histologic assessment of their cervix identical to that described for PAP + PAP. Women who test positive for high-risk oncogenetic HPV and who have a negative, unsatisfactory, ASCUS or LSIL result on LBC are retested with LBC and HPV-DNA in 6 months with the follow-up process repeated three times (total of 2 years of follow-up). Women who repeatedly test positive for high-risk oncogenetic HPV and who have a negative, unsatisfactory, ASCUS or LSIL result on LBC are retested with LBC at the end of their 2-year follow-up are immediately referred to colposcopy and biopsy for histologic assessment of their cervix identical to that described for PAP + PAP.

HPV + LBC + HPV/LBC-age (age restriction). The screening and testing protocol is identical to HPV + LBC + HPV/LBC with the exception that only women 30 years of age or older receive a HPV-DNA test for primary screening. Women younger than 30 years of age receive LBC + HPV + LBC.

Economic Evaluation

A cohort simulation Markov model was developed to determine from a health systems perspective (i.e., health ministry) the cost-effectiveness of the 21 alternative CC screening strategies in terms of both their costs and health outcomes. All analyses were conducted using Microsoft Excel 2003 and TreeAge Pro Suite (TREEAGE Software Inc; Williamstown, MA, USA).

Model

The model was based on the progression of HPV and CC carcinogenesis illustrated in Figure 1 (epidemiologic model). The

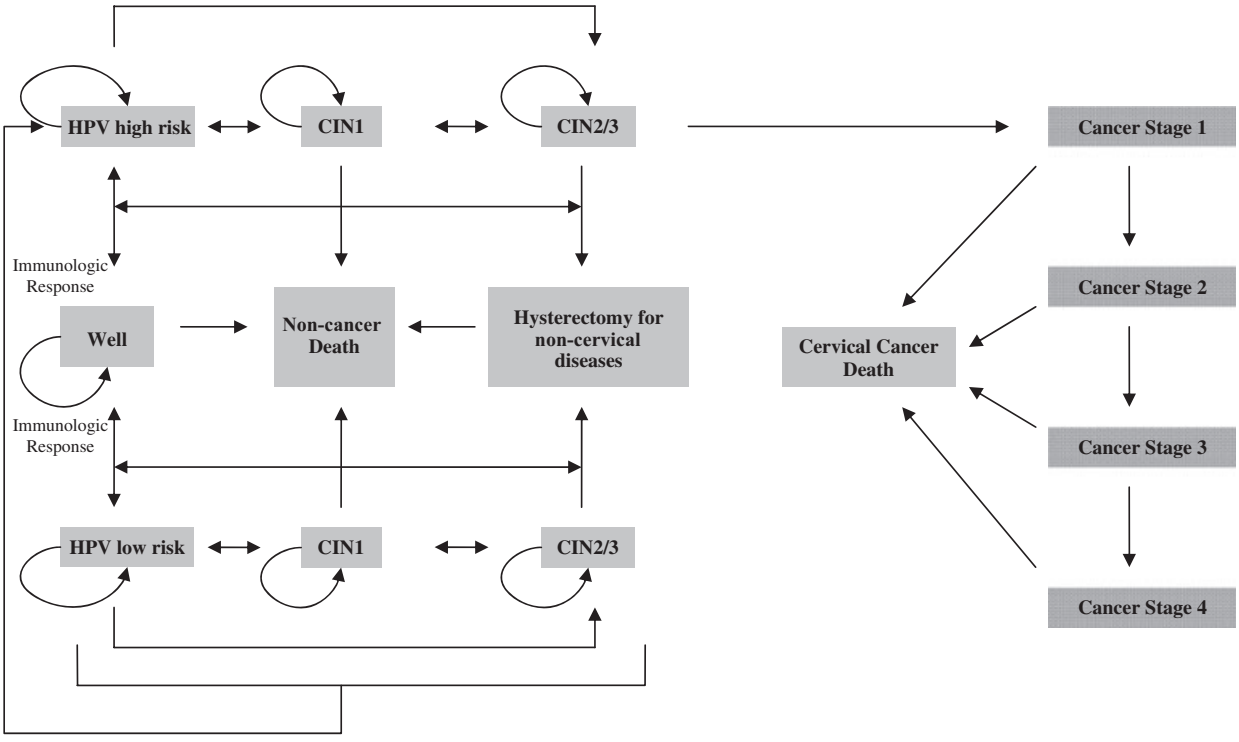


Figure 1 Progression of human papillomavirus (HPV) and cervix carcinogenesis. CIN, cervical intraepithelial neoplasia.

model starts with women 12 years of age in the well state (clear of infection) and as they increase in age, they can acquire low-risk HPV (i.e., will never develop into CC) or high-risk oncogenetic HPV (i.e., can potentially develop into CC). The cohort was followed until age 80. Each cycle in the model represents 1 year. Each year, age-dependent probabilities for death (all cause) and hysterectomy are applied and these women are censored from further analysis (i.e., removed from the pool at risk). The remaining women either remain in their current health state or transition to another health state.

Once infected with HPV, CIN on the cervix can develop, which range in severity from CIN1 to CIN2/3. Only CIN caused by a high-risk oncogenetic HPV strain can potentially lead to CC. However, prior to CC, the condition can spontaneously regress to a lesser severity or clear completely. Women who clear the HPV infection are assumed to develop an immunologic response, thereby reducing their chance of future infection. Once CC develops, no regression can occur to a better health state and in each year a cancer-specific mortality rate is applied. However, CC mortality rates differ between women with detected and treated cancers compared to women with undetected and untreated cancers. Treatment for cancer consists of conization, hysterectomy, pelvic lymphadenectomy (removal of the pelvic lymph nodes), chemotherapy, and radiation. Women surviving for longer than 5 years after CC treatment are considered cured but do not return to routine screening.

Each screening and testing algorithm is applied to the epidemiologic model. Depending on the screening interval and age of the women (screening does not begin until age 18), age-specific coverage rates are applied to determine the number of women who will receive primary screening. Women who are not screened continue to progress and regress into other health states. Women who are screened also continue to progress and regress into other health states while progressing through the screening and testing algorithm. Hence, progression through the screening/testing algorithm are dependent on the health status at the time the test was applied (e.g., well, CIN2/3, and cancer), the sensitivity and specificities of the various tests, the specific testing algorithm and the number of women who are not lost to follow-up (i.e., compliance). For example, for women with no histologic abnormalities (i.e., <CIN1) a result of ASCUS or worse on PAP or LBC is a false positive. However, in the following years she may get infected with HPV and develop CIN2/3, and if tested again, a result of ASCUS or worse on PAP or LBC is considered a true positive. Alternatively, if her CIN2/3 was caused by low-risk HPV strain, and she was tested with HPV, a positive result is a false positive. Alternatively, if her CIN2/3 were caused by a high-risk oncogenetic HPV strain, a positive result is a true positive.

Furthermore, at 2- and 3-year screening intervals, women who are not screened (i.e., missed) return to routine screening using 1-year screening intervals and 1-year coverage rates, given that these women are eligible to receive screening immediately. It is important to note that in the model, women who are incompliant with follow-up or women who receive two sequential unsatisfactory samples are assumed to return to routine screening. It is also assumed that colposcopy and biopsy is the diagnostic gold standard for confirming the presence and grade of CIN and the presence and severity of CC.

Hence, based on the characteristics of each test (e.g., sensitivity and specificity) and when they are applied in each algorithm, the testing and diagnostic outcomes for women as they progress and regress in HPV infection over time is generated. Therefore the differences in the test characteristics of each test and how each test is applied in each algorithm will generate a different set of costs and health outcomes and forms the basis of the comparative analysis.

Model inputs. All modeling assumptions and their sources are shown in Tables 1 and 2. The simulation model was based on the underlying epidemiology associated with the progression of HPV and CC carcinogenesis. Alberta-specific epidemiologic data included CC incidence, CC prevalence, and aggregated CC mortality. There was no Alberta-specific data on the incidence of HPV infection and age-specific high-risk HPV incidence rates were derived from the published Canadian literature [3]. Obtaining Alberta-specific incidence rates for high-risk oncogenetic HPV infection was generated by recalibrating the HPV incidence rates (obtained from the literature) to match the CC prevalence rates generated by the model to actual Alberta CC prevalence data. This process was conducted iteratively under the current Alberta screening/testing algorithm (i.e., 1-year PAP + PAP) until the estimated age specific CC prevalence rates from the model matched closely with the actual CC prevalence rates of Alberta.

Furthermore, although Alberta-specific CC mortality was available, it did not differentiate the increase risk in mortality as CC increased in severity (i.e., Stage 1 CC vs. Stage 4 CC). Stage-specific CC mortality rates were derived from the published Canadian literature [3]. Obtaining Alberta-specific mortality rates was generated by recalibrating stage-specific CC mortality rates to match the CC mortality rates generated from the model to the aggregate Alberta-specific CC mortality data.

Costs. All costs were made to reflect 2007 Canadian dollars and discounted at a rate of 5%. Testing costs were provided by Calgary Laboratory Services and Capital Health. Physician, Outpatient, and Inpatient costs for other diagnostic procedures and treatments were extracted from three Alberta provincial health ministry databases. The Alberta Physician Claims database provided information related to billing services and ministry payments to physicians for medically insured services in Alberta. For 2004–2005, physician cost data for procedures related to CC screening/testing were provided based on physician fee codes associated with CC screening/testing. However, for each service event, other procedures listed with the CC screening/testing procedures were recorded and an average cost for the procedure related to CC screening/testing calculated. The objective was to obtain the most representative cost estimate for the services associated with CC screening/testing and including other procedures listed ensured that the analysis account for physicians routinely conducting and billing for other services that accompany the procedure of interest.

Physician fee codes were then used to identify procedures and costs related to CC screening/testing for outpatient and inpatient services using a conversion table that translated the physician fee codes into their corresponding outpatient and inpatient service codes. The Alberta Discharge Abstracts database provided cost information related to hospital inpatient procedures while the Ambulatory Care Classification database provided cost information related to outpatient procedures for 2004–2005. In both databases, for each service event, other procedures listed with the CC screening/testing procedures were recorded and an average cost for the procedure related to CC screening/testing calculated.

Outcomes. Quality-adjusted life years (QALYs) were used as the primary measurement for assessing cost-effectiveness between the alternative screening/testing algorithms. CC cases, CC deaths, and QALY are interrelated in that a greater number CC cases will be positively associated with a greater number of

Table 1 Age-specific model inputs

Parameter	Age (years; values are per 1000 population)															Source
	12	15	18	20	25	30	35	40	45	50	55	60	65	70	75	80	
All cause mortality	0.18	0.24	0.37	0.39	0.39	0.47	0.74	1.0	1.5	2.5	3.2	6.1	10.3	16.4	26.5	43.2	[3]
All cause hysterectomy	0	0	0	0	0	7	13	29	35	92	84	86	144	137	126	127	*
Screening coverage 1 year	0	0	0	582	653	622	566	606	488	535	538	502	496	259	237	136	*
Screening coverage 2 years	0	0	0	657	747	745	684	728	664	659	674	658	594	398	337	167	*
Screening coverage 3 years	0	0	0	731	842	868	802	850	839	783	810	813	693	537	436	198	*
HPV incidence HR	33	125	192	42	140	197	111	36	31	19	65	112	199	199	199	33	†
HPV incidence LR‡	49	183	282	62	206	289	162	53	46	28	95	165	293	293	293	49	[3]
IC incidence	0	0	0	0.03	0.14	0.19	0.17	0.18	0.12	0.09	0.13	0.12	0.15	0.13	0.003	0.007	§
QALY HPV clear	0.94	0.94	0.94	0.94	0.94	0.94	0.94	0.93	0.93	0.92	0.92	0.91	0.91	0.91	0.91	0.88	[3]

Note: Values listed are approximate.
*Canadian Community Health Survey Cycle 3.1 http://www.statcan.ca/english/concepts/health/cycle3_1/overview.htm.
†Calibrated to reflect Alberta epidemiology. Values were generated by iteratively recalibrating age-specific high-risk HPV incidence rates until there was congruence between actual Alberta prevalence and model estimated prevalence of cervical cancer.
‡HR HPV incidence was scaled upwards based on HR : LR ratio from Krahn et al. [3].
§The Alberta Cancer Board Alberta Registry Database (September 2008).
HPV, human papillomavirus; HR, high-risk; IC, invasive cancer; LR, low-risk; QALY, quality-adjusted life years.

CC deaths with both contributing to reduce the total number of QALYs. QALYs were discounted at a rate of 3%.

Model simulations and uncertainty. It is important to provide information regarding the degree of variability (i.e., uncertainty) in potential costs and effectiveness to enable decision makers to evaluate the *credible* range of potential costs and outcomes. Expected values of costs and effectiveness were calculated from 6000 Monte Carlo simulations using the distributions and standard errors listed in Table 2. During each simulation, for each input with a fitted distribution, a value is randomly sampled from the distribution and the costs and effectiveness were calculated for the simulation (probabilistic sensitivity analysis). Based on the 6000 sample sets, a distribution of expected costs and effectiveness for each alternative is generated from which the degree of uncertainty is assessed.

Criteria for cost-effectiveness. Both a health economic and a CC screening policy perspective were used to determine cost-effectiveness. Alternatives that were less effective than the current algorithm were not considered cost-effective because they would increase CC cases and deaths. That is, from a CC screening policy perspective, alternatives that generate greater CC cases and deaths were unacceptable alternatives. Alternatives that were less costly and more effective compared to other alternatives were considered cost-effective. The cost-effectiveness of alternatives that were more costly and more effective were deemed uncertain because they are ultimately dependent on whether decision makers deem the additional effectiveness is worth the additional cost; although $50,000 per additional QALY gained was used as a relative benchmark.

Cost attribution analysis. Cost attribution analysis (CAA) is an approach that examines the systematic differences in costs between alternatives to not only elucidate the relative resource implications on disparate health sectors but to also identify the cost drivers (i.e., cost attributing) driving the cost differences. Presenting conventional economic evaluation results (e.g., incremental cost-effectiveness ratio [ICER]) with information generated via CAA would provide decision makers with information that identifies cost-effective alternatives while also providing insight into where resources from within the system can be potentially shifted to facilitate the adoption of the cost-effective alternative.

There are four primary budgetary areas related to CC screening. These are resources related to the screening tests (including primary and follow-up testing), physician consultations, outpatient procedures (e.g., colposcopies, biopsies, and conizations), and inpatient procedures (e.g., cancer treatment). Accordingly, the model was calibrated to track and categorize costs by these budgetary categories. Within each category, alternative screening strategies were contrasted in terms of their cost impacts and the percent change calculated within each category.

Results

All costs are expressed in 2007 Canadian dollars. All results are per woman.

Economic Evaluation

Figure 2 shows the relative cost-effectiveness between the 21 CC screening/testing algorithms evaluated. Compared to the current Alberta screening/testing algorithm of 1-year PAP + PAP, algorithms that were more effective included: 3-year LBC + HPV + LBC-age; 3-year PAP + HPV + PAP-age; 1-, 2-, and 3-year LBC + HPV + LBC; 1 and 2-year LBC + HPV + LBC-age; 1-, 2-

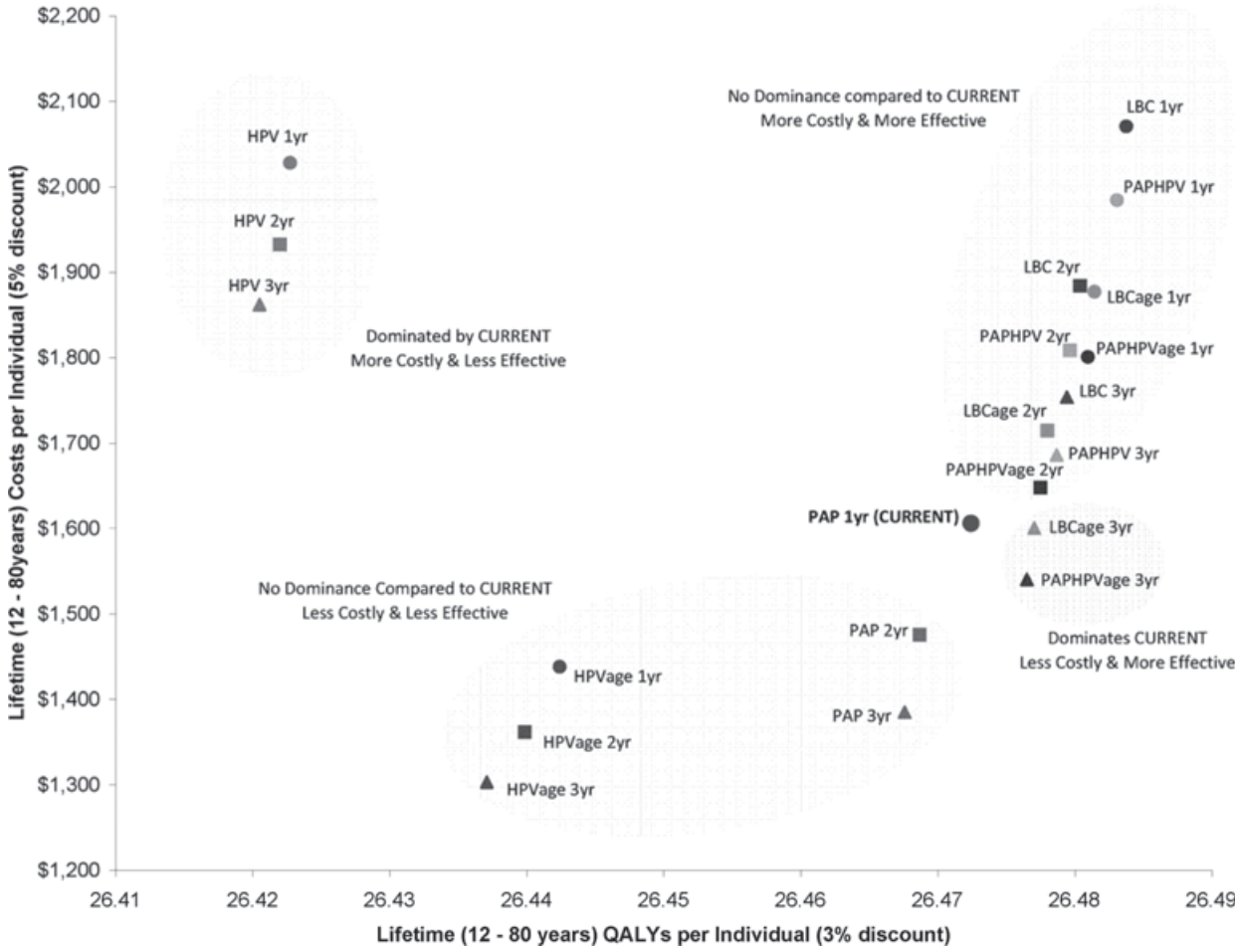
Table 2 Model inputs

Model parameters	Input	SE or range	Distribution*	Source
Cervical cancer (CC) screening program				
Screening follow up participation rate	0.76	0.5–0.9	Uniform	[3]
Natural progression of HPV infection				
From HPV low-risk strain to:				
CIN1 low-risk strain	0.028	0.01–0.046	Uniform	[16]
CIN2/3 low-risk strain (<35 years old)	0.0035	0.001–0.006	Uniform	[17]
CIN2/3 low-risk strain (≥35 years old)	0.0145	0.004–0.025	Uniform	[17]
Well/clear	0.126	0.018–0.233	Uniform	[16]
From HPV high-risk strain to:				
CIN1 high-risk strain	0.045	0.01–0.08	Uniform	[16]
CIN2/3 high-risk strain (<35 years old)	0.0035	0.001–0.006	Uniform	[17]
CIN2/3 high-risk strain (≥35 years old)	0.0145	0.004–0.025	Uniform	[17]
Well/clear	0.126	0.018–0.234	Uniform	[16]
From CIN1 low-risk strain to:				
CIN2/3 low-risk strain	0.045	0.04–0.05	Uniform	[16]
HPV low-risk strain	0.101	0.085–0.116	Uniform	[3]
Well/clear	0.325	0.11–0.54	Uniform	[3]
From CIN1 high-risk strain to:				
CIN2/3 high-risk strain	0.10	0.08–0.12	Uniform	[16]
HPV high-risk strain	0.112	0.062–0.162	Uniform	[3]
Well/clear	0.325	0.11–0.54	Uniform	[3]
From CIN2/3 low-risk strain				
CIN1 low-risk strain	0.068	0.023–0.113	Uniform	[3]
HPV low-risk strain	0.02	0.01–0.03	Uniform	[3]
Well/clear	0.002	0.001–0.003	Uniform	[3]
From CIN2/3 high-risk strain				
CIN1 high-risk strain	0.017	0–0.034	Uniform	[3]
HPV high-risk strain	0.02	0.01–0.03	Uniform	[3]
Well/clear	0.002	0.001–0.003	Uniform	[3]
From CC				
Stage 1 to stage 2	0.148	0.212–0.340	Uniform	[17]
Stage 2 to stage 3	0.293	0.226–0.360	Uniform	[17]
Stage 3 to stage 4	0.397	0.309–0.484	Uniform	[17]
Partial immunity to HPV low risk after clearance	0.61	0.32–0.90	Uniform	[3]
Partial immunity to HPV high risk after clearance	0.38	0.18–0.58	Uniform	[3]
Characteristics of CC				
Symptomatic stage 1	0.144	0.109–0.179	Uniform	[17]
Symptomatic stage 2	0.212	0.162–0.261	Uniform	[17]
Symptomatic stage 3	0.504	0.399–0.609	Uniform	[17]
Symptomatic stage 4	0.685	0.561–0.809	Uniform	[17]
Stage 1 survival with treatment†	0.997	0.993–1	Uniform	[17]
Stage 2 survival with treatment†	0.982	0.973–0.991	Uniform	[17]
Stage 3 survival with treatment†	0.831	0.771–0.890	Uniform	[17]
Stage 4 survival with treatment†	0.627	0.596–0.657	Uniform	[17]
Adjustment for survival—without treatment	0.03	—	None	‡
Characteristics of screening tests and treatment				
PAP sensitivity	0.74	0.055	Beta	[3]
When in stage CIN1				
ASCUS	0.364	—	None	[3]
LSIL	0.461	—	None	[3]
HSIL	0.1758	—	None	[3]
When in stage CIN2/3 or invasive cancer				
ASCUS	0.173	—	None	[3]
LSIL	0.244	—	None	[3]
HSIL	0.583	—	None	[3]
PAP specificity	0.868	0.064	Beta	[3]
Has no histological abnormalities				
False ASCUS	0.682	—	None	[3]
False LSIL	0.242	—	None	[3]
False HSIL	0.076	—	None	[3]
Proportion of inadequate samples	0.0058	0.0001	Beta	[3]
LBC sensitivity (difference between LBC–CC)	0.0643	0.064	Normal	[3]
When in stage CIN1				
ASCUS	0.364	—	None	[3]
LSIL	0.461	—	None	[3]
HSIL	0.176	—	None	[3]
When in stage CIN2/3 or invasive cancer				
ASCUS	0.173	—	None	[3]
LSIL	0.244	—	None	[3]
HSIL	0.583	—	None	[3]
LBC specificity	–0.0402	0.081	Uniform	[3]
Has no histological abnormalities				
False ASCUS	0.682			
False LSIL	0.242			
False HSIL	0.075			
Proportion of inadequate samples	0.0024	0.0001	Beta	[3]

Table 2 Continued

Model parameters	Input	SE or range	Distribution*	Source
HPV hybrid II				
Sensitivity high-risk strain ≥30 years	0.948	0.020	Beta	[18]
Specificity high-risk absence ≥30 years	0.860	0.021	Beta	[18]
Sensitivity ratio high-risk strain <30 years§	1.070	0.046	Gamma	[18]
Specificity ratio high-risk absence <30 years§	0.860	0.021	Gamma	[18]
Treatment effectiveness				
Loop electrical excision procedure (LEEP) conization	0.964	0.014	Beta	[19]
Outcomes—quality-adjusted life years				
Well/clear (age-specific, refer to Table 1)				
CIN1	0.91	—	None	[3]
CIN2/3	0.87	—	None	[3]
Cervical cancer stage 1 without treatment	0.65	0.49–0.81	Uniform	[3]
Cervical cancer stage 2 without treatment	0.67	0.44–0.90	Uniform	[3]
Cervical cancer stage 3 without treatment	0.56	0.42–0.70	Uniform	[3]
Cervical cancer stage 4 without treatment	0.48	0.36–0.60	Uniform	[3]
Cervical cancer stage 1 with treatment	0.86	0.73–0.99	Uniform	[3]
Cervical cancer stage 2 with treatment	0.83	0.68–0.98	Uniform	[3]
Cervical cancer stage 3 with treatment	0.83	0.68–0.98	Uniform	[3]
Cervical cancer stage 4 with treatment	0.63	0.47–0.78	Uniform	[3]
Outcomes discount rate	0.03	—	NA	
Costs				
General practitioner visit	$82.58	—	None	[20]
Chest x-ray	$120	—	None	[20]
Tests and diagnostics				
PAP (labor, equipment, supplies)	$22.00	—	None	‖
LBC (labor, equipment, supplies)	$14.36	—	None	¶
HPV (labor, equipment, supplies)	$40.76	—	None	¶
Colposcopy (none are conducted as inpatient)				
Physician	$50.42	$15.77	Gamma	#
Outpatient	$294.70	$191.97	Gamma	**
Cone biopsy				
Physician	$31.13	$11.4	Gamma	#
Outpatient (none are conducted as inpatient)	$270.72	$78.45	Gamma	**
Punch biopsy				
Physician	$127.96	$31.29	Gamma	#
Outpatient (none are conducted as inpatient)	$276.01	$128.61	Gamma	**
Proportion conducted as punch	0.85	—	None	#
CO2 laser therapy				
Physician	$119.25	$23.52	Gamma	#
Outpatient (none are conducted as inpatient)	$211.16	$178.28	Gamma	**
LEEP				
Physician	$118.18	$13.30	Gamma	#
Outpatient (none are conducted as inpatient)	$295.52	$174.51	Gamma	**
Proportion conducted as LEEP	0.73	—	None	#
Chemotherapy				
Physician	$257.23	$245.38	Gamma	#
Inpatient (none are conducted as outpatient)	$13,800.33	$8,415.18	Gamma	††
Radiation				
Physician	$374.05	$297.93	Gamma	#
Inpatient (none are conducted as outpatient)	$10,838.41	$8,374.97	Gamma	††
Pelvic lymphadenectomy				
Physician	$267.63	$122.26	Gamma	#
Inpatient (none are conducted as outpatient)	$7,314.70	$1,146.56	Gamma	††
Hysterectomy				
Physician	$356.36	$173.19	Gamma	#
Outpatient	$816.97	$488.08	Gamma	**
Inpatient	$4,597.93	$2,655.69	Gamma	††
Proportion done as inpatient	0.45	—	None	††
End-of-life cost for cancer (1 year prior to death)	$44,070	$22,035–$88,140	Uniform	[3]
Cost discount rate	0.05	—	NA	

*Refers to the mathematical distribution assigned to incorporate the likelihood of possible values (i.e., inherent variance) of the input during model simulation. "None" means that input does not vary during model simulation. Distributions are fitted based on primary data. In general, parameters estimated from larger sample sizes generate smaller ranges of possible values (consistent with statistical theory). Therefore inputs with very small standard errors (SE) indicate they were fitted from large sample sizes.
†Original values were adjusted to generate Alberta-specific mortality rates during model validation Final adjusted values are shown.
‡The Alberta Cancer Board Alberta Registry Database (September 2008). Derived by comparing women who received immediate initial treatment with women who whose initial treatment information show "none," "refuse," "unknown," "observation," or missing in Alberta Cancer Registry databases.
§Sensitivity and specificity for women under 30 years of age is calculated by dividing the sensitivity and specificity for women ≥30 years of age by the ratio.
‖Calgary Laboratory Services Accounting Records, pers. comm., 2008.
¶Capital Health Laboratories Planning Information, pers. comm., 2008.
#Alberta Health and Wellness Physician Claims Data Base 2004–2005. Values were adjusted to reflect 2007 Canadian dollars using the Consumer Price Index.
**Alberta Health and Wellness Ambulatory Care Classification System 2004–2005. Values were adjusted to reflect 2007 Canadian dollars using the Consumer Price Index.
††Alberta Health and Wellness Discharge Abstracts Database 2004–2005. Values were adjusted to reflect 2007 Canadian dollars using the Consumer Price Index.
ASCUS, atypical squamous cells of undetermined significance; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; HSIL, high-grade squamous intraepithelial lesion; LBC, liquid-based cytology; LSIL, low-grade squamous intraepithelial lesion; NA, not applicable; PAP, Papanicolaou's smear test.



PAP: PAP+PAP (CURRENT)
PAPHPV: PAP+HPV+PAP
PAPHPVage: PAP+HPV+PAP-age
LBC: LBC+HPV+LBC
LBCage: LBC+HPV+LBC-age
HPV: HPV+LBC+HPV/LBC
HPVage: HPV+LBC+HPV/LBC-age.

Figure 2 Cost-effectiveness of alternative cervical cancer screening and testing algorithms. HPV, human papillomavirus; LBC, liquid-based cytology; PAP, Papanicolaou's smear test; QALYs, quality-assisted life years. Shaded areas indicate those alternatives that are extended dominated. The different symbols are to differentiate the alternatives.

and 3-year PAP + HPV + PAP; and 1- and 2-year PAP + HPV + PAP-age.

Of the algorithms that generated greater effectiveness, 2- and 3-year PAP + HPV + PAP, 2-year PAP + HPV + PAP-age, 2- and 3-year LBC + HPV + LBC, and 1-, 2-, and 3-year LBC + HPV + LBC-age were extended dominated (i.e., dominated by other algorithms that provided equal effectiveness at a cheaper cost) (Fig. 3). Compared to 1-year PAP + PAP, 3-year PAP + HPV + PAP-age will save $16,078 per additional QALY gained. Subsequently, 1-year PAP + HPV + PAP-age, 1-year PAP + HPV + PAP, and 1-year LBC + HPV + LBC will cost $58,512, $86,266, and $127,076 per additional QALY gained, respectively.

Uncertainty. Greater than 98% of simulations for 2- and 3-year PAP + PAP and 1-, 2-, and 3-year HPV + LBC + HPV/LBC-age were less costly and less effective (Fig. 4) compared to 1-year PAP + PAP. Greater than 60% of simulations for 1-, 2-, and 3-year PAP + HPV + PAP; 1-year PAP + HPV + PAP-age; 1-, 2-, and 3-year-LBC + HPV + LBC; and 1- and 2-year LBC + HPV + LBC-age were more costly and more effective. Greater than 88% of simulations for 1-, 2-, and 3-year HPV + LBC + HPV/LBC were less effective and more costly. For 3-year PAP + HPV + PAP-age and 3-year LBC + HPV + LBC-age, 63% and 45%, respectively, were less costly and more effective.

Differential Resource Impacts

Figure 5 shows the incremental cost between 1-year PAP + PAP and the alternative algorithms that were equally or more

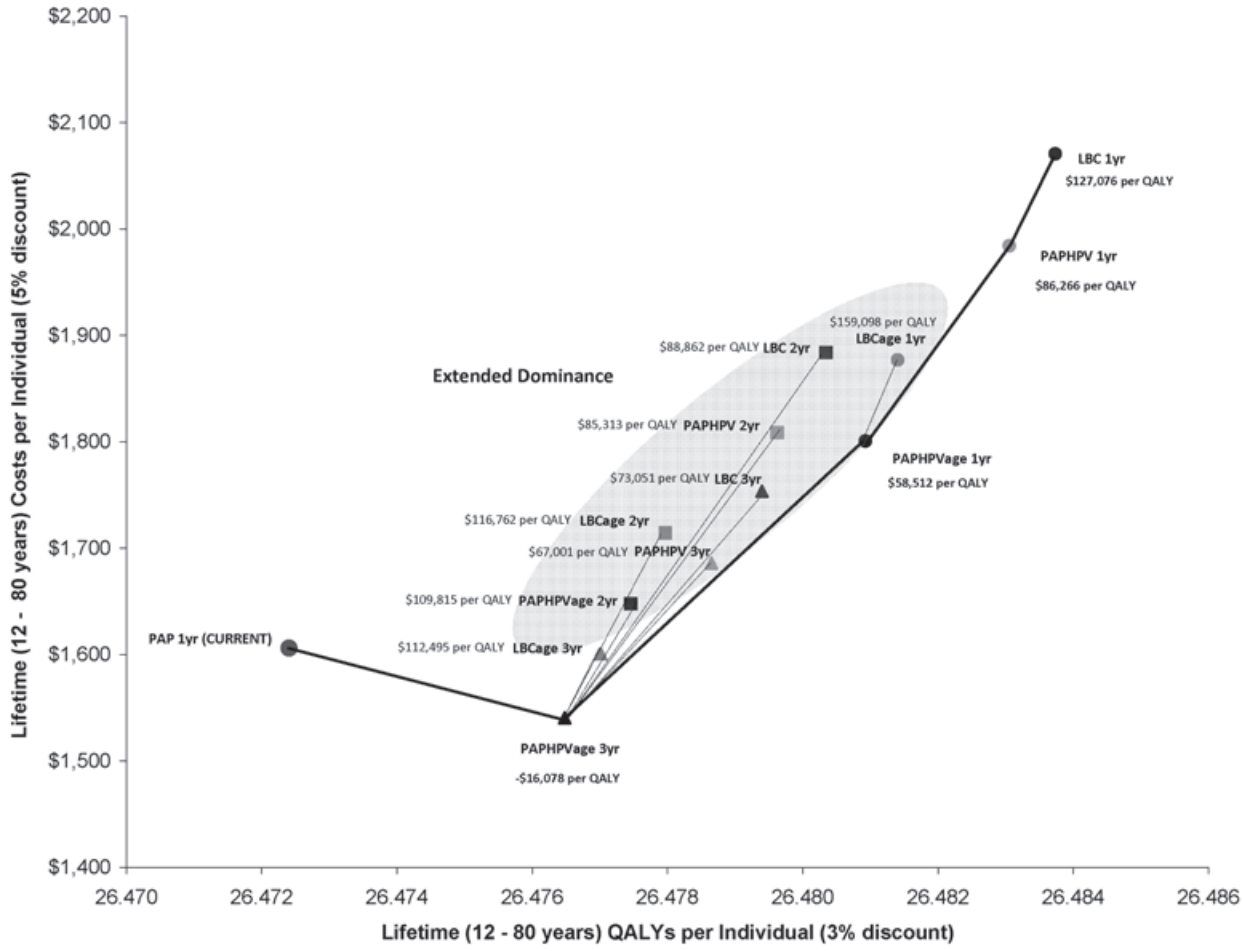


Figure 3 Cost-efficiency curve of alternative cervical cancer screening and testing algorithms. HPV, human papillomavirus; LBC, liquid-based cytology; PAP, Papanicolaou's smear test; QALYs, quality-assisted life years. Shaded areas indicate those alternatives that are extended dominated. The different symbols are to differentiate the alternatives.

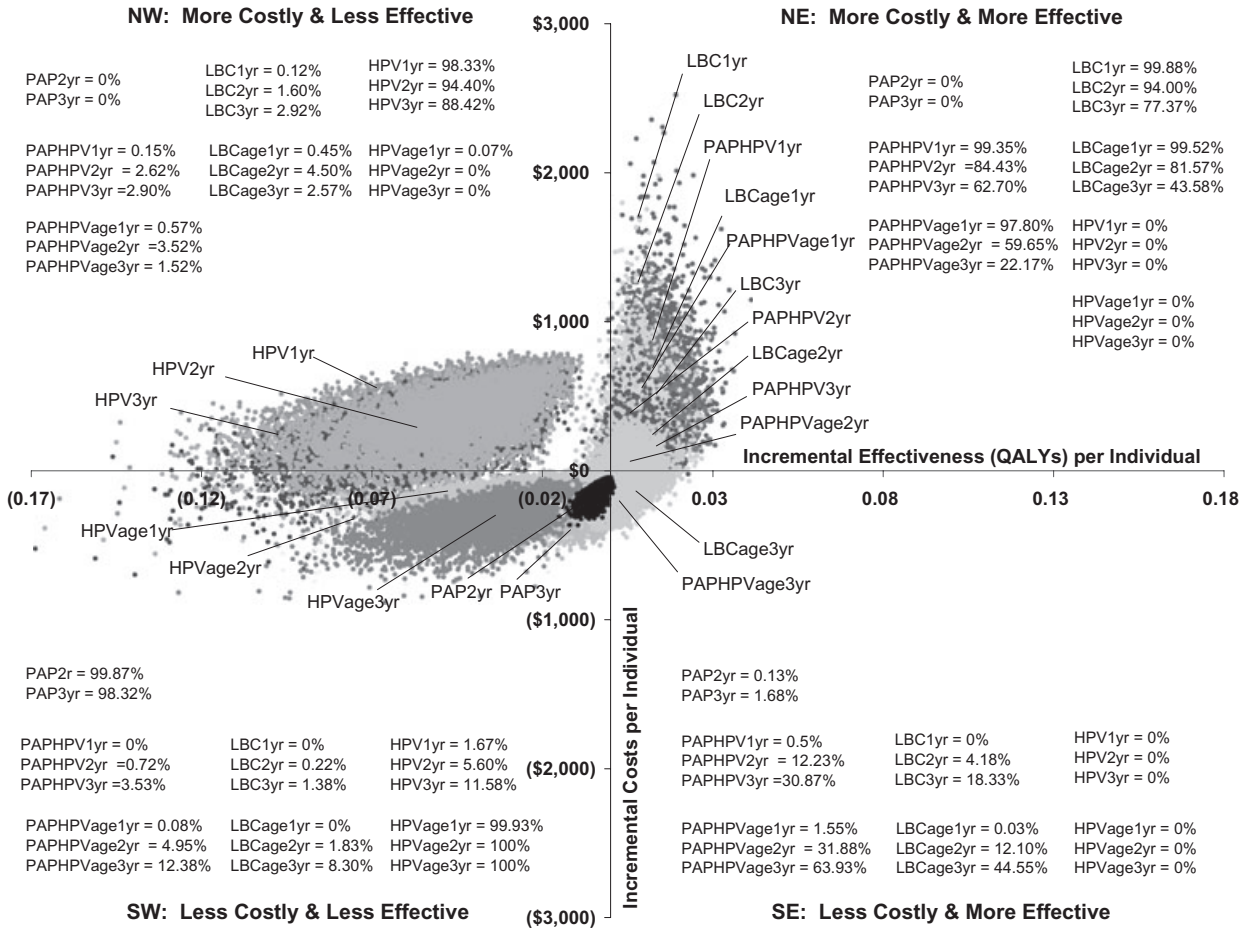
effectively separated into four cost categories: testing, physician, inpatient, and outpatient services. Three-year PAP + HPV + PAP-age are estimated to generate a net cost decrease of 4.2%. The net cost decrease is completely driven by a reduction in testing and physician costs of 22.1% and 18.6%, respectively. There is a cost increase of 0.8% and 27.7% in inpatient and outpatient services, respectively. Three-year LBC + HPV + LBC-age are estimated to generate a cost decrease of 0.3%. The net cost decrease is completely driven by a reduction of 19.4% in physician services. There is a cost increase of 19.6% in testing, 0.9% in inpatient, and 30% in outpatient services. PAP + HPV + PAP and LBC + HPV + LBC at all screening intervals, and PAP + HPV + PAP and LBC + HPV + LBC at 1- and 2-year screening intervals, are estimated to generate a net cost increase. There are no cost decreases to any cost categories.

Discussion

Value for Money

After eliminating alternatives that were not cost-effective or unacceptable from a CC program policy perspective, four alternatives remained for final consideration, which includes (listed in order of increasing effectiveness): 3-year PAP + HPV + PAP-age, 1-year PAP + HPV + PAP-age, 1-year PAP + HPV + PAP, and 1-year LBC + HPV + LBC. Compared to the current Alberta CC screening/testing algorithm, 3-year PAP + HPV + PAP-age was less costly and more effective translating in a cost saving of –$16,078 per additional QALY gained per women. Thus, 3-year PAP + HPV + PAP-age are cost-effective.

Achieving subsequent levels of effectiveness would require switching to 1-year PAP + HPV + PAP-age followed by 1-year



PAP: PAP+PAP (CURRENT)
PAPHPV: PAP+HPV+PAP
PAPHPVage: PAP+HPV+PAP-age
LBC: LBC+HPV+LBC
LBCage: LBC+HPV+LBC-age
HPV: HPV+LBC+HPV/LBC
HPVage: HPV+LBC+HPV/LBC-age

Figure 4 Distribution of incremental costs and outcomes of alternative cervical cancer screening and testing algorithms compared to the current Alberta screening algorithm (1-year PAP + PAP). Six thousand Monte Carlo simulations were conducted for each screening/testing algorithm. For each simulation, incremental costs and effectiveness were calculated between the current Alberta Screening/Testing algorithm and the other 21 alternative screening/testing algorithms being considered. The graph illustrates the percentage of simulation falling in each quadrant (northwest [NW], northeast [NE], southeast [SE], and southwest [SW]) on the incremental cost-effectiveness plane. Costs and outcomes are discounted at 5% and 3%, respectively. HPV, human papillomavirus; LBC, liquid-based cytology; PAP, Papanicolaou's smear test; QALYs, quality-assisted life years.

PAP + HPV + PAP and 1-year LBC + HPV + LBC with ICERs of $58,512, $86,266, and $127,076, respectively, per additional QALY gained per women. Whether these are cost-effective is dependent on whether decision makers deem the additional health gain worth the additional cost. However, these ICERs exceed conventional cost-effectiveness thresholds suggested in the health economic literature (e.g., ≥$50,000 per additional QALY gained).

Affordability and Policy Implications

Several economic evaluations comparing alternative CC screening algorithms have been published in the extant literature [5–14]. While these studies identify whether alternatives are more/less costly and more/less effective, they do not provide any indication of the resource impacts to disparate sectors of the health system from which decision makers can use to strategize

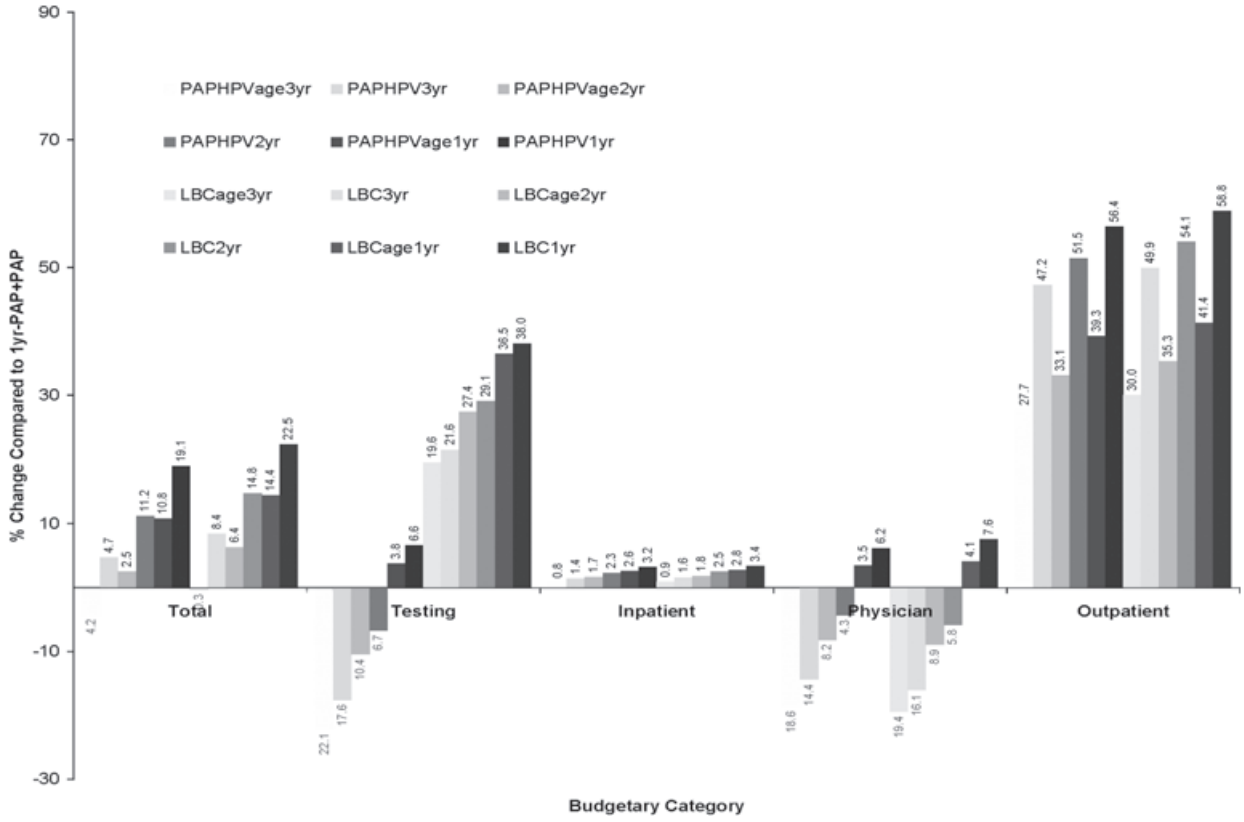


Figure 5 Percent change (compared to 1-year PAP + PAP) in costs by budgetary category. HPV, human papillomavirus; LBC, liquid-based cytology; PAP, Papanicolaou's smear test.

around potential resource shifting. Although 3-year PAP + HPV + PAP-age was found to generate a 4.2% decrease in total costs, decision makers should be cognizant of the cost increases of 0.8% and 27.7% to inpatient and outpatient services, respectively. Budgetary resources can potentially be shifted from testing and physician services to fund the additional resource requirements for inpatient and outpatient services.

Study Limitations

The results however, should be evaluated in light of the following limitations. First, the results are entirely founded on the screening and testing algorithms outlined in this report. Yet, it is uncertain how clinicians will ultimately use these tests. Although in actual conditions there will be variation in how these tests are used depending on clinical presentation and patient history, the screening/testing algorithms outlined in this report should be adhered to the greatest extent clinically permissible in order to achieve the economic and health outcomes described. Still, it is important to note that the analysis was based on Canadian costs that limit the generalizability of results to other health settings.

Second, uniform distributions were used to characterize the transition probabilities from CIN to CC because the extant literature provided ranges opposed to actual empirical data from which a distributional form could be fitted to the parameters. Consequently, the transition probabilities may not be representative of the transition probabilities that characterizes CC carcinogenesis. Nonetheless, the probabilistic sensitivity analysis did indicate that the results were consistent.

Third, women undergoing cancer screening may not receive any benefit and may in fact be exposed to iatrogenic health risks (e.g., unnecessary invasive follow-up procedures resulting from either false positive biopsies or CIN graded 2 or 3 that would have naturally regressed) [15]. The costs and health outcomes associated with iatrogenic events were not considered in the analysis because colposcopy-guided biopsy was considered the gold standard in actual clinical practice.

Conclusion

There are tradeoffs in costs and improvement in health outcomes associated with each CC screening/testing algorithm. For instance, increasing screening interval decreases total costs but results in greater CC cases and deaths. LBC and HPV have a higher sensitivity but lower specificity than PAP, resulting in

increased follow-up and confirmatory testing of both appropriate (true positive) and inappropriate (false positive) referrals. Identifying the CC screening/testing algorithm that provides the best balance between costs and improvements in health outcomes for women requires careful consideration of not only which test is used (PAP, LBC, or HPV) but at which stage in the screening/testing process (e.g., primary, triage, or follow-up) would it provide the greatest benefit. All this, while taking into account age, risk, and the progression and regression of HPV infection. Among the 21 algorithms considered, 3-year PAP + HPV + PAP-age emerges as the algorithm that provides the best balance and offers the best value for money.

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