ORIGINAL CONTRIBUTION

Cost-effectiveness of the Conventional Papanicolaou Test With a New Adjunct to Cytological Screening for Squamous Cell Carcinoma of the Uterine Cervix and Its Precursors

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Objective: To estimate costs and outcomes of conventional annual Papanicolaou (Pap) test screening compared with biennial Pap test plus speculoscopy (PPS) screening for cervical neoplasms.

Design: A Markov model compared cost-effectiveness and outcomes of annual Pap tests with biennial PPS. The model includes direct costs of screening, diagnostic testing, and treatment for squamous intraepitheial lesions and invasive cancers; indirect costs (eg, lost productivity because of cervical cancer); and newer management practices, including human papillomavirus DNA testing.

Patients: Women aged 18 to 64 years.

Intervention: Screening for cervical neoplasms with either annual Pap smear test or biennial PPS.

Main Outcome Measure: Marginal cost per life-year gained.

Results: The probability of women having squamous intraepithelial lesions, cervical cancer, or death from cervical cancer was lower among women undergoing PPS biennially. A total of 12 additional days of life per woman was gained with biennial PPS during the 47-year model period. Total average cumulative direct medical costs per patient were $1419 for biennial PPS compared with $1489 for annual Pap tests. Total costs, including direct medical costs and indirect costs, were $2185 for PPS compared with $3179 for Pap tests alone. Increased savings and patient outcomes were observed in high-risk populations.

Conclusion: Our simulations indicate that biennial screening with PPS is expected to provide cost savings for women older than 18 years compared with annual Pap test screening, especially for those in high-risk populations.

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CERVICAL CANCER is a largely avoidable cause of death.[1] Yet, the American Cancer Society[2] estimates that in 1999 there were 12 800 incident cases of cervical cancer and 4800 cervical cancer deaths in the United States alone. Squamous cell carcinomas, accounting for 85% to 90% of all cervical cancers,[3] have an extended latency period. The vast majority of cervical squamous cell carcinomas can be prevented with early detection and treatment of high-grade squamous intraepithelial lesions (HSILs).

The primary test used to screen for precancerous abnormalities and cervical cancer is the Papanicolaou (Pap) test. Since the introduction of the Pap test in the 1930s, cervical cancer mortality has declined by 70% in the United States and in other countries with near-universal screening programs.[4-6] Although 59% of women in the United States undergo annual screening and 80% undergo biennial screening,[7] the death rate from cervical cancer has remained virtually constant since the mid-1980s. A number of factors contribute to this plateau, including increasing numbers of high-risk women who are not regularly screened, sexual activity at a younger age, and infection with the human papillomavirus (HPV).

See Editor's Comment at end of article

The sensitivity and specificity of Pap tests vary widely, from 11% to 99% and 14%

METHODS

Our model projected costs and health outcomes for 3 cohorts of women: (1) 18-year-old women followed up to age 65 years or death from cervical cancer or other causes; (2) 18-year-old women followed up to age 44 years or death; and (3) 45-year-old women followed up to age 65 years or death. These age groups reflect current screening recommendations and acknowledge the relationship between severe pathology and older age.

DEVELOPMENT OF THE MODEL

The health states for the Pap and PPS arms were designed to reflect the cytological results, histological diagnosis, and management practices associated with abnormal screening results with Pap tests alone vs PPS. Women with an abnormal screening result who have undergone subsequent histological diagnosis are followed up in different states than women who have only undergone cytological screening. There are slightly different disease management options associated with PPS, resulting in minor variations between the Pap and PPS Markov health states. Finally, because PPS is a biennial program, a Markov health state was included for women who either are disease negative or have undetected disease during the years that PPS is not performed.

MODEL STRUCTURE

A Markov model was used to simulate the natural course of 2 hypothetical cohorts of women. One cohort is screened annually with Pap tests alone (the Pap arm); the other cohort is screened biennially with Pap test plus a speculoscopy examination (the PPS arm). Each cycle of the model represents 1 year; women are followed up for a maximum of 47 cycles (ages 18 to 64 years).

Initially, identical cohorts of women enter through the screening state and attend the screening in both the Pap and PPS arms. Noncompliance for both arms was included in this model on the basis of figures from the Centers for Disease Control and Prevention. A proportion of women will not attend annual screening or will not pursue follow-up screens after abnormal results are obtained.[7]

This model assumes that, since squamous intraepithelial lesions (SILs) are asymptomatic, women are identified only from abnormal screening results. However, invasive cervical cancer (ICC) may be symptomatic; women with ICC are assumed to undergo screening and staging and proceed to the ICC Markov state.

DISEASE INCIDENCE AND MANAGEMENT

Women who undergo screening are classified as having abnormal or normal screening results. They are further stratified into true disease-negative, true disease-positive, false-negative, and false-positive categories (**Figure 1** and **Figure 2**). This model assumes that an abnormal screening result leads to further clinical investigation. After the initial cycle, the rate of abnormal screening results in the PPS arm was calculated on the basis of the difference between SIL and cancerous disease detected through biennial PPS screening and annual Pap screening. The percentage of women with abnormal screening results in the PPS arm was conservatively assumed to plateau at 6%, the rate used in the Pap arm. The rate of abnormality in the PPS arm was adjusted because more women in the PPS cohort are detected with cervical abnormalities at the initial screening. Therefore, the pool of women with disease decreases for each subsequent cycle.

Women who have false-positive results incur the cost of subsequent diagnostic workups (colposcopy). Women who have true-positive results are stratified on the basis of the result of the screening program. For the Pap arm, women may have screening results of atypical squamous cells of undetermined significance (ASCUS), LSIL, HSIL, or ICC. For the PPS arm, women may have screening results of Pap normal–speculoscopy positive; Pap ASCUS–speculoscopy positive or negative; Pap LSIL–speculoscopy positive or negative; Pap HSIL–speculoscopy positive or negative; and Pap cancer–speculoscopy positive or negative.

Women who have positive screening results may undergo histological diagnosis or may receive a series of follow-up cytological screening tests. After histological diagnosis or cytological screens, patients proceed to the appropriate nonscreening health states for treatment and/or cytological follow-up. Women who have true-positive results and are cytologically followed up may not adhere with their recommended follow-up screening regimen.[15] For example, only 68% of women with a conventional ASCUS Pap test result return for follow-up care. Women with true-positive results undergoing histological diagnosis are distributed into states of LSIL, HSIL, and ICC on the basis of their biopsy result.[16] Women with a negative Pap test, positive speculoscopy result, and positive biopsy test are assumed

to 97%, respectively.[8-11] In a large meta-analysis of cross-sectional studies that used histological findings as the reference standard, Fahey et al[12] calculated the mean sensitivity of Pap tests for detecting cervical abnormalities at 58% in screening populations and 66% in follow-up populations.

During the past 5 years, numerous adjuncts to Pap tests have become available. By improving the sensitivity of screening tests, adjuncts have the potential to further reduce cervical cancer morbidity and mortality. Speculoscopy with the use of the Speculite (Trylon Corporation, Torrance, Calif), the only new in vivo adjunct approved by the Food and Drug Administration, involves magnified visual examination of the cervix and vaginal canal by a physician or qualified technician with the use of chemiluminescent light to detect abnormalities. A study by Mann et al[13] of 29 women found that the combination

to have a disease course similar to that of women with positive Pap test and positive biopsy results, since this is unknown. The main differences in the model between post-Pap and post-PPS management is the option of HPV-DNA triage testing for an ASCUS test result included in the Pap arm (see **Table 1** and **Table 2** for the specific management patterns and associated costs).

Management patterns after ASCUS and LSIL Pap test results vary widely, depending on the patient's previous Pap test history and risk factors for cervical cancer, and the physician's belief in the likelihood of ASCUS and LSIL regression. Consequently, for the base-case model, we assumed that 50% of all Pap tests with a diagnosis of LSIL will immediately be followed up with colposcopy, endocervical curettage, and biopsy and 50% will be cytologically screened every 6 months for 18 months. For Pap tests with an ASCUS diagnosis, 45% of patients will undergo immediate histological diagnosis, 45% will be followed up cytologically, and 10% will undergo HPV triage testing for high-risk HPV DNA. These options were included because, in the real world, physicians have varying philosophies on the management of ASCUS and LSIL Pap test results.

DATA SOURCES

Probabilities

With the exception of the screening tests' positive and negative predictive values and the percentage of women attending the screening visit (annual vs biennial), all clinical variables used in both arms of the model are identical. These variables are presented in **Table 3**.

To the extent possible, clinical outcomes based on histological examination were preferred over cytologically based data. Numerous data sources were used to obtain these values.[20-24] Rates of cervical cancer were derived from SEER (Surveillance, Epidemiology, and End Results Program) data.[26] Five-year survival after cervical cancer treatment as well as treatment cure rates for LSIL and HSIL were obtained from 2 sources.[27,28] Overall death rates and life expectancy by 5-year age group and race were taken from life tables obtained from the National Center for Health Statistics.[29]

Direct Medical and Indirect Costs

Direct medical costs were based on average Medicare reimbursement values derived from 2 data sources (Table 2 and **Table 4**). A 3% annual discount rate was used for the base-case analysis.[30]

Indirect costs relate to lost earnings resulting from time lost, disability, and mortality attributable to cervical cancer screening, SIL, and cervical cancer. The model assumes that women lose 2 hours for each cervical cancer screening and 4 hours for each colposcopy, endocervical curettage, and biopsy. Individuals who were histologically diagnosed and treated for LSIL and HSIL lost 1.6 days per year[31]; women with cervical cancer reported 35.4 lost days per year. Indirect costs associated with cervical cancer screening, SIL, and cancer were calculated by multiplying hours lost by a blended median hourly earning rate derived from data from the Bureau of Labor Statistics.[32]

Mortality costs reflect productivity losses after cervical cancer deaths. This method takes into consideration life expectancy at age of death[29] and changing patterns of earnings at successive ages. Output losses were obtained from a study of the lifetime costs of injury (Dorothy P. Rice, ScD [Hon], professor emeritus, Institute for Health and Aging, University of California, San Francisco, written communication, September 1997). A 3% discount rate was used.[30]

MODEL OUTCOMES AND SENSITIVITY ANALYSIS

The primary model outcome is the marginal cost per life-year gained (cost-effectiveness) with PPS as compared with Pap screening. Secondary outcome measures include (1) the probability of developing ICC and cervical cancer death; (2) the probability of detecting SILs; (3) total discounted direct medical costs; and (4) total discounted direct medical and indirect costs.

Cost-effectiveness was examined separately on the basis of direct medical costs and combined direct medical plus indirect costs. Four health effects were modeled: (1) years of life gained, (2) cases of invasive cancer avoided, (3) SILs detected, and (4) cervical cancer deaths avoided.

Sensitivity analyses evaluated the robustness of the following clinical variables: probability of undergoing annual screening, probability of returning for 6-month examinations, annual discount rate, management of ASCUS and LSIL Pap tests, and disease progression and regression rates. We also tested the impact of targeting screening to a high-risk population that included alteration of clinical variables (percentage of women with abnormal screening results and likelihood of being high-risk HPV positive), decreased attendance of screening examinations, and increased rates of cervical cancer.

of Pap test plus speculoscopy (PPS) identified 83% of women with significant pathological findings compared with 31% for Pap tests alone. Wertlake et al[14] reported that the addition of speculoscopy to the Pap test resulted in finding 34% more women with HSIL (which includes cervical intraepithelial neoplasia [CIN] 2, CIN3, and carcinoma in situ) and 81% more women with low-grade squamous intraepithelial lesions (LSIL) (which includes HPV positive and CIN1) than with the Pap test alone; however, speculoscopy added no confirmatory power to positive Pap smears.

The goal of this study was to estimate the costs and outcomes of annual conventional Pap test screening compared with biennial PPS. Because most cervical cancers are squamous cell carcinomas, this model only examines the outcomes and costs of squamous abnormalities.

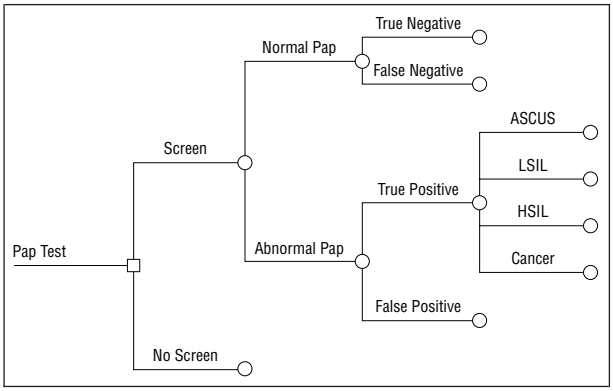

Figure 1. *Papanicolaou (Pap) test (screening state). ASCUS indicates atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; and HSIL, high-grade squamous intraepithelial lesion.*

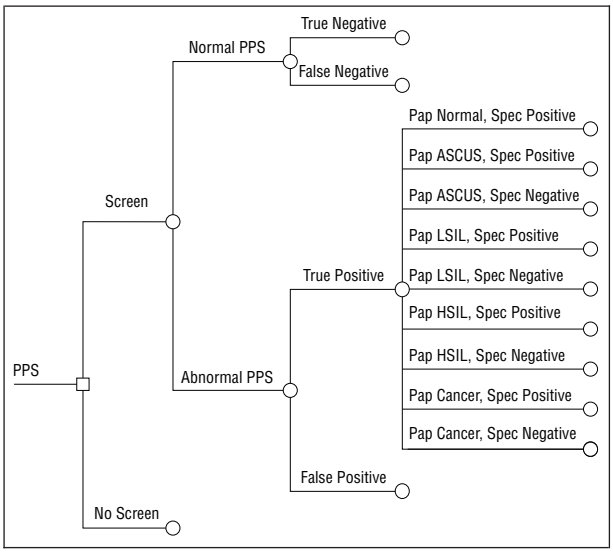

Figure 2. *Papanicolaou (Pap) test plus speculoscopy (PPS) (screening state). Spec indicates speculoscopy; ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; and HSIL, high-grade squamous intraepithelial lesion.*

RESULTS

BASE-CASE ANALYSES

Table 5 presents the cumulative percentage of women detected with histologically confirmed SILs and cervical cancer in both the Pap and the PPS arms, as well as the associated costs. Initially, the incidence of LSILs was higher in the PPS arm than the Pap arm (0.9% vs 0.7% in the 18- to 64-year-old cohort, respectively). However, in all 3 age cohorts, more SILs, cases of cervical cancer, and cervical cancer deaths occurred in the Pap arm over time. These results indicate that detecting and treating true disease associated with ASCUS or LSIL Pap test results reduces lead-time bias for cervical cancer detection. Table 5 also shows that total direct medical costs associated with screening, treatment, and follow-up were slightly higher for all 3 cohorts in the Pap arm.

Table 1. Management Options Based on Abnormal Screening Test Results*

Pap Arm	PPS Arm
ASCUS 1. 3 Follow-up cytological screenings 2. Colposcopy/ECC/biopsy 3. HPV-DNA testing	Pap ASCUS—speculoscopy positive 1. Colposcopy/ECC/biopsy Pap ASCUS—speculoscopy negative 1. PPS screen in 6 mo
LSIL 1. 3 Follow-up cytological screenings 2. Colposcopy/ECC/biopsy	Pap LSIL—speculoscopy positive *or* Pap LSIL—speculoscopy negative 1. 1 Follow-up PPS screening in 6 mo 2. Colposcopy/ECC/biopsy
HSIL 1. Colposcopy/ECC/biopsy	Pap HSIL—speculoscopy positive *or* Pap HSIL—speculoscopy negative 1. Colposcopy/ECC/biopsy
Cancer 1. Colposcopy/ECC/biopsy	Pap cancer—speculoscopy positive *or* Pap cancer—speculoscopy negative 1. Colposcopy/ECC/biopsy Pap negative—speculoscopy positive 1. PPS screen in 6 mo 2. Colposcopy/ECC/biopsy

**Pap indicates Papanicolaou test; PPS, Pap plus speculoscopy; ASCUS, atypical squamous cells of undetermined significance; ECC, endocervical curettage; HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; and HSIL, high-grade squamous intraepithelial lesion.*

A year-by-year analysis of the direct medical costs associated with screening, treatment, and follow-up for the 18- to 64-year-old cohorts showed that the annual costs of PPS were higher initially because of increased detection of SILs at an earlier stage. At age 18 years, the direct medical costs were $78 for PPS vs $54 for Pap alone. However, the costs of Pap become higher over time as more cases of HSIL and cancer develop in the Pap arm. After the threshold point at 31 years of age, the cumulative per-patient costs of Pap increases to $1489 by age 63 years compared with $1419 for PPS.

Table 6 shows the percentage of SIL and cervical cancer cases avoided with biennial PPS screening. For all 3 cohorts, there were fewer cases of LSIL, HSIL, and ICC in the PPS arm. Because of earlier disease detection, there were also fewer deaths from cervical cancer in the PPS arm. Table 6 also presents costs and life-years gained. The PPS regimen resulted in lower direct medical costs for screening, treatment, and follow-up in all 3 cohorts modeled for the base-case analyses. The discounted gain in life expectancy ranged from 8.0 to 12.8 days. The lower costs of PPS and greater life expectancy gained suggest that the PPS regimen is more beneficial than the conventional annual Pap test screening regimen.

Table 2. Estimated Unit Costs of Medical Services Used in Model*

Type of Resource	CPT Code/ DRG	Average Medicare Reimbursement in 1997, $
Cervical screening (excludes physician time)		
Papanicolaou smear	88156	25.00
Speculoscopy		18.50
Physician visits		
Physician visit, new patient, level 2 (initial screen visit)	99202	490.00
Initial consultation	99205	129.00
Physician visit, established patient, level 2 (follow-up screen visits)	99212	27.00
Stage IA: age 40 y or older	99213	39.00
Physician visit, established patient, level 5 (histological workups)	99215	93.00
Physician visit, inpatient, day 1, level 2	99222	111.00
Physician visit, inpatient, days 2+, level 2	99232	52.00
Treatment service for treating squamous intraepithelial lesions		
Cryosurgery		118.00
Cone biopsy		1097.00
LEEP		305.00

**Costs are derived from* American Medical Association CPT '96, Professional Edition[17] *and* St. Anthony's DRG Optimizer.[18] *CPT indicates Current Procedural Terminology; DRG, diagnosis related group; and LEEP, loop electrosurgical excision procedure.*

SENSITIVITY ANALYSIS

Health Outcomes

The percentage of women with abnormal screening results had the most substantial impact on the model (**Table 7**). In the Pap arm, the risk of cervical cancer in the 18- to 64-year-old cohort varied from 0.6% to 0.8%, with the percentage of women with abnormal screening results varying from 4% to 8%. In the PPS arm, the risk of cervical cancer did not vary substantially by increasing the percentage of women with abnormal screening results; however, the risk of LSIL and HSIL increased. Increasing the regression rate resulted in less SIL and cancerous disease; however, overall life-years gained did not change. Finally, there was little effect on life-years gained and cost with an increase or decrease in the use of colposcopy, endocervical curettage, and biopsy.

Costs

Sensitivity analyses varying the discount rates from 0% to 6% changed the total costs in both arms but not the life-years gained (Table 7). Since biennial PPS screening resulted in fewer cases of cervical cancer, increasing the costs of cervical cancer screening resulted in a greater marginal difference between the 2 treatment arms.

Table 3. Clinical Variables Used in Cost-effectiveness Model*

Variable	Base Case	Source (Reference)
Probability of attending annual screening	0.58	7
Probability of attending biennial screening	0.80	7
Probability of not returning for follow-up		
ASCUS	0.30	15
LSIL	0.30	15
HSIL	0.22	15
Probability of abnormal results of screen		
Pap	0.06	16
PPS	0.12	14
Positive predictive value		
Pap	0.44	19
PPS	0.29	
Negative predictive value		
Pap	0.95	19
PPS	0.99	
Regression rates		
With ASCUS Pap	0.51	20-22
With LSIL Pap	0.46	23
Probability of screening ASCUS and high-risk HPV	0.53	24

	Base Case		
	<35 y	≥35 y	
Screening results, Pap			25
ASCUS	0.84	0.92	
LSIL	0.11	0.04	
HSIL	0.05	0.04	
Cervical cancer	0	0.003	
Screening results, PPS			25
Pap normal, speculoscopy positive	0.47	0.37	
Pap ASCUS, speculoscopy positive	0.11	0.09	
Pap ASCUS, speculoscopy negative	0.33	0.49	
Pap LSIL, speculoscopy positive	0.02	0.01	
Pap LSIL, speculoscopy negative	0.04	0.02	
Pap HSIL, speculoscopy positive	0.012	0.011	
Pap HSIL, speculoscopy negative	0.016	0.015	
Pap cancer, speculoscopy positive	0	0.0016	

**LSIL indicates low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; Pap, Papanicolaou test; PPS, Pap plus speculoscopy; ASCUS, atypical squamous cells of undetermined significance; and HPV, human papillomavirus.*

High-Risk Populations

Table 8 shows health outcomes and costs associated with cervical cancer screening in a high-risk population. Among high-risk women, fewer SILs will be detected and a great-

er percentage of women will develop or die of cervical cancer than in the general screening population. In the sensitivity analysis, the percentage of women who tested positive for HPV in the Pap arm varied from 0% to 78%. The incidence of SIL and cancer increased and decreased, respectively, with the percentage of HPV-positive women. The direct medical costs incurred by high-risk women were lower than for the normal screening population, since fewer women incur screening costs and more women will die of cervical cancer, no longer accruing costs.

COMMENT

Economic modeling is increasingly used to estimate the "real-world" cost-effectiveness of comparative therapeutic interventions. Economic models can measure the impact of medical interventions in terms of health care costs and patient benefits during periods beyond those of clinical trials and other prospective studies. Models are also generalizable to a variety of settings, allowing a wide range of environments and patient populations to be assessed.

Certain assumptions were made in the development of our model. First, the model assumes that women who are treated twice for a single SIL are cured; those receiving only 1 treatment may or may not be cured. Cured women reenter the screening pool after their second treatment follow-up period and can develop lesions again at the same likelihood as other women. Second, pregnant women are treated no differently in the model for Pap ASCUS and Pap LSIL, since cytological management is taken into consideration. If a pregnant woman has a cytological result of HSIL or cancer, treatment is delayed until the birth of the child. Since treatment still takes place within the same Markov cycle, no adjustment for pregnancy was made. Third, the model assumes that all unscreened women with ICC will become symptomatic by the end of a cycle and will be treated accordingly. Finally, the model assumed that only women diagnosed as having ICC would undergo hysterectomy.

This study is subject to a number of limitations. First, it does not take into account any effects of cervical cancer screening programs on patient quality of life. The increased sensitivity of PPS leads to a greater proportion of SILs being detected, but the decision to treat immediately vs following cytologically is controversial, and the impact on the affected woman's quality of life is unknown. Additionally, the impact of a false-positive screening result on the quality of life was not accounted for in this model, nor was the impact on the woman's quality of life of developing cervical cancer and of cervical cancer treatment.

Because of the lack of available data specific to PPS, the rates of disease progression and regression were assumed to be the same in the Pap and PPS arms. We were also unable to age-adjust many of the clinical variables

Table 4. Estimated Costs of Treating Cervical Cancer*

Treatment Service	Average Cost per Patient, $
Stage IA	
Conization	1097
Simple hysterectomy	7423
Stage IB-IIA	
Radical hysterectomy/pelvic lymphadenectomy	10 504
Radiation	9798
Stage IIB	
Radiation	9798
Stage III	
Radiation	6436
Stage IV	
Radiation	6436
Palliative care	1820

**Excludes 5-year follow-up. Costs are derived from* American Medical Association CPT '96, Professional Edition[17] *and* St. Anthony's DRG Optimizer.[18]

Table 5. Base Case: Cumulative Percentage of Women Developing SIL and Cervical Cancer as Well as Associated Costs*

	Age, y					
	18-44 (Followed Up 27 y)		45-64 (Followed Up 20 y)		18-64 (Followed Up 47 y)	
	Pap	PPS	Pap	PPS	Pap	PPS
Health outcomes, % of women						
Developing LSIL†	21.05	10.54	15.13	7.42	36.39	16.27
Developing HSIL†	7.44	3.31	5.22	2.35	12.71	5.12
Developing cervical cancer	0.30	0.10	0.31	0.11	0.68	0.21
Dying of cervical cancer	0.12	0.04	0.13	0.05	0.30	0.10
Average cumulative cost per woman, 1997 US$						
Direct medical costs‡	1100	1039	863	832	1489	1419
Total direct medical and indirect costs‡	2177	1587	1558	1226	3179	2185

**SIL indicates squamous intraepithelial lesion; Pap, Papanicolaou test; PPS, Pap plus speculoscopy; LSIL, low-grade squamous intraepithelial lesion; and HSIL, high-grade squamous intraepithelial lesion.*

†*Cases histologically confirmed by colposcopy, endocervical curettage, and biopsy.*

‡*Costs discounted at 3% rate annually.*

Table 6. Base Case: Incremental Analysis of the Biennial PPS Screening Regimen Compared With Annual Conventional Papanicolaou Test Screening*

Effects	Age, y		
	18-44	45-64	18-64
Cases avoided, %			
LSIL	10.5	7.7	20.1
HSIL	4.1	2.9	7.6
Cervical cancer	0.30	0.20	0.47
Cervical cancer deaths	0.08	0.08	0.08
Life-years gained, d†	8.0	10.6	12.8
Costs, $			
Direct medical costs†	(61)	(31)	(70)
Direct plus indirect medical costs†	(590)	(332)	(994)
CE ratio			
Direct costs per life-year gained	PPS dominates	PPS dominates	PPS dominates
Direct plus indirect costs per life-year gained	PPS dominates	PPS dominates	PPS dominates

**Numbers in parentheses indicate negative values, ie, cost savings. PPS indicates Papanicolaou test plus speculoscopy; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; and CE, cost-effectiveness.*

†Costs and life-years gained are discounted at a 3% rate annually.

associated with disease regression and progression, as well as histological diagnosis after colposcopy, endocervical curettage, and biopsy. Because of the limited data sources available for certain model variables, extensive sensitivity analyses were conducted to examine the impact of these variables on the overall model results.

There are many studies evaluating the cost-effectiveness of cervical cancer screening[33-36]; however, direct comparison with other models is difficult. Studies vary in the populations examined and type of model as well as variable values. Most models published in peer-reviewed literature are limited to analyses of the cost-effectiveness of the conventional Pap test method, although in the past 3 years, several researchers have evaluated the cost-effectiveness of the new in vitro adjuncts to conventional Pap test screening. The primary end point in these studies is the number of life-years saved. Many of the models do not report differences in the rate of identification of LSILs and HSILs.

Two of the most widely cited models are those of Eddy[37] and Fahs et al.[38] Eddy designed a 9-state Markov model to evaluate the cost-effectiveness of alternative conventional Pap test screening regimens.[37] Among women aged 20 to 75 years, the marginal cost per year of life saved ranged from $10 000 (for a screening regimen every 4 years compared with no screening) to $262 800 (for a screening regimen every 2 years compared with screening every 3 years) to greater than $1 million (for a screening regimen every year compared with screening every 2 years).

Fahs et al[38] used a similar approach to evaluate the cost-effectiveness of Pap tests for elderly women. Compared with no screening, the cost per year of life gained ranged from $1666 for screening 1 time at 65 years of age to $5956 for a screening regimen every 3 years to $33 693 for an annual screening regimen. Mandelblatt and Fahs[39] reported separately on the cost-effectiveness of a conventional Pap test screening

Table 7. Sensitivity Analysis: Incremental Life-Years Gained and Costs*

	Incremental Life-Years Gained (PPS–Pap)	Incremental Costs (PPS–Pap), $
Probabilities		
4% Abnormal Pap screening rate	4.7	52
8% Abnormal Pap screening rate	17.2	(189)
19% Abnormal PPS screening rate	11.3	(23)
ASCUS and LSIL disease regression 50% greater	11.7	(70)
ASCUS and LSIL disease regression 50% lower	13.5	(56)
Management		
Immediate referral to colposcopy for 75% of Pap ASCUS or LSIL smears	12.8	(106)
Immediate referral to colposcopy for 25% of Pap ASCUS or LSIL smears	13.1	(54)
Costs		
0% Discount rate direct medical	12.8	(166)
6% Discount rate direct medical	12.8	(28)
0% Discount rate direct plus indirect medical	12.8	(1997)
6% Discount rate direct plus indirect medical	12.8	(1161)
Cervical cancer treatment 50% higher	12.8	(102)
Cervical cancer follow-up 50% lower	12.8	(57)
Cervical cancer follow-up 50% higher	12.8	(82)

**Numbers in parentheses indicate negative values, ie, cost savings. Pap indicates Papanicolaou test; PPS, Pap plus speculoscopy; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; and ASCUS, atypical squamous cells of undetermined significance.*

Table 8. High-Risk Population: Probability of SIL and Cervical Cancer Associated With Annual Conventional Papanicolaou (Pap) Test Screening and Biennial PPS Screening*

	PPS Arm		Pap Arm			
	Base Case	High-Risk HPV Positive, 53%	Base Case	High-Risk HPV Positive, 53%	High-Risk HPV Positive, 0%	High-Risk HPV Positive, 78%
Probability of LSIL,† %	16.3	14.1	36.4	20.5	19.9	20.8
Probability of HSIL,† %	5.1	4.4	12.7	7.2	6.6	7.4
Probability of cervical cancer, %	0.21	0.3	0.68	0.6	0.5	0.6
Probability of cervical cancer death, %	0.10	0.13	0.30	0.27	0.25	0.28
Direct medical costs, $	1419	1246	1489	1160	1152	1163

*SIL indicates squamous intraepithelial lesion; PPS, Pap test plus speculoscopy; HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; and ASCUS, atypical squamous cells of undetermined significance. The following baseline variables were modified to examine a population deemed to be at high risk: (1) overall risk of death; (2) compliance with initial screen: 0.59 for Pap and 0.74 for PPS; (3) follow-up compliance with abnormal ASCUS, LSIL, and HSIL screens: 0.28, 0.26, and 0.20, respectively; and (4) probability of high-risk HPV after ASCUS: 0.78.

†Cases histologically confirmed by colposcopy, endocervical curettage, or biopsy.

program that targets low-income elderly women. Among infrequently screened elderly women, the cost savings of a cervical cancer screening program was $5907 per 100 Pap test tests performed, and 3.72 years of life were gained for every 100 Pap tests performed.

There has been substantial controversy associated with the cost-effectiveness of the new in vitro adjuncts to conventional Pap test screening. Using a model similar to the Fahs model, Schechter[40] reported a cost of $48 474 per life-year gained among women screened biennially with PAPNET. The Blue Cross Blue Shield Technology Evaluation Center recently published an update of their previous clinical assessment of the new in vitro adjuncts (ThinPrep [Cytyc, Boxborough, Mass], AutoPap [Neopath, Redmond, Wash], and Papnet [Neuromedical Systems, Inc, Upper Saddle River, NJ]); they concluded that none of these new technologies was cost-effective compared with conventional Pap test screening.[41]

This model comparing conventional, annual Pap test screening with PPS screening has several unique attributes. It is a cost-effectiveness model for cervical cancer screening that incorporates HPV triage testing for ASCUS tests. Second, it compares annual conventional Pap test screening with a biennial Pap test screen accompanied by an in vivo adjunct technology. Third, the model uses the positive and negative predictive values of Pap test and PPS rather than the sensitivity and specificity of the conventional Pap test. Fourth, it incorporates several different management options for the abnormal test results—watchful waiting, repeating the cytological examination, and referring the patient directly to undergo colposcopy. Fifth, the data used to support the variable values for the positive and negative predictive values are based on histological reference standards, not cytological results that have been reproduced by repeated cytological examination. Finally, the model includes both the direct and indirect costs associated with cervical cancer screening and treatment for SIL.

There is agreement in the medical community that the vast majority of cases of squamous cell carcinoma of the cervix can be prevented with early detection. The biennial PPS screening program enables health care providers to detect more SIL than with conventional annual Pap test screening. This is especially important for women in high-risk populations who are more likely to be noncompliant with regular screening regimens and follow-up visits. Therefore, adding the speculoscopy to routine Pap test screening results in fewer cases of cervical cancer, fewer deaths from cervical cancer over time, and more life-years gained for a lower cost. Using the PPS screening program will result in better health outcomes and cost savings over time. The PPS screening is cost-effective and should be considered as a useful adjunct to the Pap test.

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Editor's Comment

Papanicolaou (Pap) smears are considered a cost-effective screening tool, but there continue to be cases of preventable cervical cancer. This study considers the potential cost-effectiveness of an alternative method of screening: combining the Pap test once every 2 years with speculoscopy compared with annual Pap tests. The techniques used in this study were excellent. The project was undertaken with the financial support of the company that produces the product. My reservation is that the original articles (references 13 and 14) from which data were obtained to complete this analysis included relatively few women with significant pathological findings. In the study by Mann et al,[13] there were 29 women with significant pathological findings (atypia with condylomatous features or cervical intraepithelial neoplasia), and in the study by Wertlake and colleagues,[14] there were 191 women with low-grade and 32 with high-grade squamous intraepithelial lesions. No carcinomas in situ were found. Of course, many Pap smears and speculoscopies had to be done to find even this number with pathological results. It is also clear that adjunct speculoscopy will markedly increase the number of false-positive diagnoses, which may have important implications for quality of life and patient interactions. Additional work should be done to verify and expand the work of these authors before widespread adoption of this technique is indicated.

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