Clinical and Cost Implications of New Technologies for Cervical Cancer Screening: The Impact of Test Sensitivity

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Abstract

Objective: **To compare the available techniques for cervical cancer screening, including several new technologies, using actual program utilization patterns.**

Study Design: **Longitudinal cohort model.**

Patients and Methods: **The model followed a cohort of 100,000 women who underwent screening from age 20 through 65 years. The model was run with a weighted average of screening intervals to model the actual utilization of the cervical cancer screening program in the United States.**

Results: **The model demonstrated that new technologies with significantly increased test sensitivity have the potential to reduce the number of cancers by 45% to 60% depending on the screening frequency in fully compliant populations. At screening intervals of 2 years or more, these new technologies had cost-effectiveness ratios below $50,000 per life-year saved. Assuming existing utilization patterns, the model predicted there would be 13.2 cancers per year in the 100,000 women screened with the conventional Pap smear, and new technologies with increased test sensitivity could reduce the annual incidence to 9.5 cancers per 100,000 women screened.**

Conclusions: **The model suggests that to achieve further dramatic reduction in cervical cancer mortality, significant improvements in test sensitivity, as reflected in the new screening technologies, may be the most realistic and cost-effective approach.**

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For editorial comment, please see page 838.

There were an estimated 13,700 cases of squamous cell cervical cancer resulting in 4900 deaths in 1998 in the United States.[1] These are not large numbers compared with many other cancers because of the widely implemented cervical cancer screening program; however, there is still room for improvement because of several inefficiencies in the cervical cancer screening program. One of these problems is the relatively low test sensitivity of the basis of the program[2,3]: the Papanicolaou (Pap) smear. Over the past several years, several new products have been approved by the Food and Drug Administration (FDA) to address the shortcomings inherent in both slide preparation and (re)screening.

The Pap smear is designed to find cytologic evidence of the precancerous stages of the squamous cells lining the outside surface of the cervix. This precancerous stage is known as a cervical intraepithelial neoplasia (CIN), a localized growth that does not penetrate the basement membrane. There are three stages of CIN: I, II, and III. Carcinoma in situ (CIS) is the final precancerous stage, where the lesion has penetrated the basement membrane but is not yet fully vascularized. In the United States it is common to remove lesions at any stage with an outpatient procedure. Once the lesion is removed, it is unlikely that cancer will develop at that location on the cervix.[4] It should be noted that "the Pap smear is not reliable in detecting endocervical glandular neoplasia" (adenocarcinoma).[4]

The recent unconditional regulatory approval of several new technologies aimed at improving the

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accuracy or decreasing the labor of cervical cancer screening has raised the question of how to deploy them in both a cost-effective and clinically efficacious manner. The ThinPrep Pap Test (Cytyc Corporation, Boxborough, MA) addresses problems in specimen preparation by providing a standardized fluid for collection and automates the process of transferring the specimen to a microscope slide. The AutoPap Primary Screening System (NeoPath Corporation, Redmond, WA) automatically screens the slides before human screening and selects the 75% most likely to contain abnormalities for subsequent screening by a cytotechnologist. The AutoPap QC 300 rescreening device (NeoPath Corporation, Redmond, WA) rescreens all slides found negative by the human screeners and flags those most likely to contain abnormalities for review by a cytotechnologist.

Several models have examined the costs and outcomes of these new technologies compared with the conventional Pap smear.[5-10] This report differs from most of the others in that it compares the new technologies with each other as well. The Brown and Garber[5] and the Agency for Health Care Policy and Research (AHCPR)[3] reports have taken this approach; however, this study and the AHCPR report are different from the Brown and Garber report in that the findings were validated using managed care organization utilization data. Nonetheless, the AHCPR report did not use that approach to show how the new technologies would affect real-world outcomes. The AHCPR study concluded that the sensitivity of the Pap smear based on studies that "verified all (or a random fraction of) test negative subjects" is approximately 51%.[3]

The current report combines the utilization data and the reported sensitivity of the Pap test[3] to predict the total number of incident cancers and the effect of changing the sensitivity on the incident cancers and life-years saved. This is critical for understanding the impact of test sensitivity on program effectiveness. Without the ability to show that the model predicts known outcomes with the current standard of care, it is impossible to rely on the predictions of the model when utilizing a new methodology.

A longitudinal cohort model was developed to analyze the effect of the FDA-approved methodologies for cervical cancer screening. The payer perspective was adopted in the analysis as only direct medical costs and health benefits were considered. The results were then compared with the documented incidence of cancer both to validate the model and to predict the real-world effect of adopting the new technologies. Understanding this effect is critical in making coverage decisions.

···METHODS ···

The model was implemented as an Excel (Microsoft Corporation, Redmond, WA) spreadsheet and utilized a time-varying Markov approach to follow a cohort of 100,000 women who began screening at the age of 20 years and were screened through the age of 65. Figure 1 is a schematic of the health states modeled.

For each year in the model, members of the cohort were assigned to a variety of health outcomes. These outcomes included death from other causes, development of cervical cancer, death from cervical cancer, cervical cancer survivor, hysterectomy for benign causes, true-negative screening, true-positive screening (CIN, CIS, or squamous cell cancer found on colposcopy), false-negative screening, and false-positive screening.

In this model all women who had a positive screening test received colposcopy and were treated appropriately. Cytology test results were generally reported in terms of the Bethesda criteria.[11] For the purposes of this model, a positive cytology result was assumed to be a finding of any one of the following:

- Low-grade squamous intraepithelial lesion (SIL)
- High-grade SIL
- Atypical glandular cells of unknown significance
- Squamous cell carcinoma
- Adenocarcinoma

Women with atypical cells of unknown significance (ASCUS) were referred for a second Pap smear within the same year. One third of these women had a finding of ASCUS or higher (ASCUS+) on the second Pap smear and received colposcopy and treatment if appropriate.

Women found to have CIN or CIS on colposcopy received treatment and were returned to the screening pool. Women who were cervical cancer survivors or who had a hysterectomy were removed from the screening pool.

In reporting the results of the model, the different screening modalities were compared with a reference strategy (conventional Pap smear screening with a 10% rescreening rate). Hence, the cost effectiveness of each of the methods is presented separately in comparison to this reference strategy.

Underlying Characteristics

The model assumed a cohort of 100,000 women entered into a cervical screening regimen at the age of 20 years. The women in the model were subject to death from all causes at the rate reported by the National Center for Health Statistics.[12] Data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review were used for the cervical cancer incidence rates and death rates from cervical cancer, as well as the stage-specific 5-year survival rates for cervical cancer.[1]

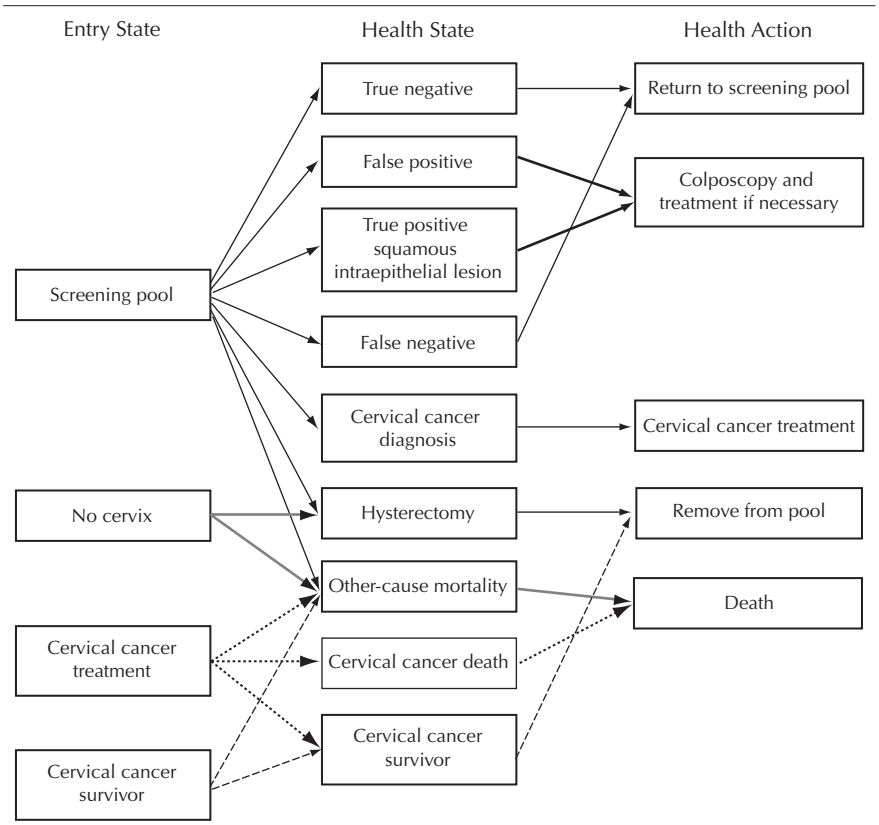
Over the course of the screening regimen, a significant proportion of the cohort underwent a hysterectomy for benign conditions. These women were no longer at risk for squamous cell carcinoma of the cervix and hence were removed from the screening pool and were modeled not to receive any further screening tests. Age-specific rates of hysterectomy as published by the Centers for Disease Control and Prevention were used to estimate the number of hysterectomies that would occur in the cohort.[13]

Natural History of Cervical Cancer

The model made certain assumptions about the course of the disease as it progressed to cervical cancer. The incidence of CIN lesions in the population was age specific, as described by Reid and Fu.[14] The mean age of women with CIN lesions was 35 years, with a peak incidence of 3550 per 100,000 women at age 29. In this model CIN lesions regressed at the rate of 65% over 6 years for women age 20-34 and at 40% over 6 years for women age 35 and older.[15,3] Thirty-five percent of CIS lesions regress over 6 years.[3] Progression proceeded in 2 stages from CIN to CIS and from CIS to cancer. Progression was modeled based on the incidence rates at each stage. Progression from CIN to CIS occurs in 6 years, whereas progression from CIS to cancer takes 10 years.[4] Ten percent of all cases of CIN that will ever progress to cancer do so within 1 year, a fact that accounts for interval cancers.[16] Cervical cancer survivors were removed from the screening pool.

The model computed the age-specific potential likelihood of CIN progressing to cancer based on the SEER incidence rates of cervical cancer,[1] the rate of CIN in the population,[14] and the age-specific rate ratio between an unscreened population and a screened population as reported by Gustafsson et al.[17] The rate ratio is the ratio of the cancer incidence in an unscreened population to the cancer incidence in a screened population. The model multiplied the SEER-reported incidence rate for 1996 adjusted for the decrease in incidence since 1987 (the year the rate ratios were calculated by Gustafsson and colleagues) by the inverse of the rate ratio.

Figure 1. Schematic of Health States and Actions in Cervical Cancer Screening Model



Movement is from left to right for each cycle to age 65 years.

Interventions

In the model, all women with positive results ([SIL], atypical glandular cells of unknown significance, cancer, or ASCUS on original smear with ASCUS+ on follow-up smear) by cervical cytology were referred for diagnostic colposcopy. The cost of diagnostic colposcopy was assumed to include the charges for *Current Procedural Terminology* (CPT)-4 codes[18] for colposcopy with biopsy(s) of the cervix (CPT code 57454) and a level IV surgical pathology examination (CPT code 88305).

All confirmed cases of CIN were further followed with treatment based on the recommendations of Kurman et al.[19] Women with CIN I were followed with cryocautery of the cervix (CPT code 57511), and women with CIN II, CIN III, or CIS were followed with a loop electrosurgical excision procedure of the cervix (CPT code 57522), including a level V surgical pathology examination (CPT code 88307).

Because of a lack of hard data regarding the actual follow-up performed on women with ASCUS, the model made the simplifying assumption that women with an ASCUS Pap smear were followed with a single follow-up Pap smear in the same year as the initial ASCUS smear. Women with a subsequent finding of ASCUS or worse in the follow-up Pap smear were referred for diagnostic colposcopy (this finding is present in 33% of the women with an initial ASCUS finding). In the base model, women with SBLB findings (**s**atisfactory for interpretation **b**ut **l**imited **b**y...)[11] were returned to the screening pool, as there are no data to show that they are treated in any special manner.

The basic model assumed that all women in the cohort were compliant with all recommendations for screening and follow-up. To demonstrate the impact of partial compliance with screening recommendations, however, the model was run at a variety of screening intervals and partial rates of compliance with recommendations for colposcopic follow-up.

Costs

Table 1 shows the costs associated with the screening methods analyzed. The reference visit at which the initial Pap smear is obtained is assumed to be general healthcare. As such, no cost was applied for these visits in the model.

The median charges to indemnity insurers for the specified CPT-4 codes were utilized for follow-up of SIL and treatment of CIN.[20] Charges were used to bias the model against new technologies that could result in more cases being forwarded to follow-up. The estimated costs for initial and end-stage treatments for cervical cancer were weighted averages of the SEER incidence rates by stage and the costs as reported by Brown and Garber.[5] The incidence by stage was assumed to be constant regardless of the screening frequency modeled. All costs are in 1997 dollars.

Screening Modalities Studied

Technologies to enhance the conventional Pap smear address 2 major sources of error: preparation error and screening error. Preparation error describes a situation in which abnormalities present with no exfoliated cells representative of disease on cervical cytology specimens. Screening error describes a situation in which abnormal cells are present on the specimen but are missed during the diagnostic process. These sources of errors are addressed separately by the new technologies as shown below:

- Conventional smears with 10% random rescreening.
- Conventional smears with AutoPap QC 300 selected rescreening.
- Conventional smears with AutoPap Primary Screening System prescreening. In this process 25% of the slides accepted by the instrument are eliminated from manual screening. There is a 15% rescreening rate for the slides that are accepted by the device.[22]
- ThinPrep Pap Test prepared slides with 10% random rescreening.

Effectiveness of Methods

It has been shown that preparation errors occur at approximately 3 times the rate of screening errors[23]; hence, the model maintained this ratio. Any methodology that relies on the conventional Pap smear will be unable to address preparation errors. Performance characteristics for improved sensitivity of the various methods were taken directly from the various manufacturers' clinical trial data for FDA submissions for proof of safety and efficacy.[22,24,25] See Table 2 for the performance characteristics of the various programs.

The percentage of slides returned is the ratio of slides from the population presented to the pre- or rescreening device that are returned for manual review. Note that the sensitivity and positive predictive value associated with manual screening methods were applied to slides that were rescreened regardless of whether they were selected for rescreening by manual or automated methods.

The sensitivity of the methods to CIN was calculated based on those slides containing abnormal cells

that were presented to each screening method. In other words, because of sampling and preparation errors, conventional Pap smears would only contain 60% of the total underlying CIN. Furthermore, the conventional smear would find 84% of CIN present on slides. This results in a combined sensitivity of 51.2%, which is comparable to the value of 51% used by the AHCPR in their recent evidence-based report.[3] For comparison with the Eddy model[16] and Brown and Garber report,[5] a combined sensitivity for CIN of 80% also was modeled, and the parameters for this analysis are shown in Table 2 in the section labeled "High Conventional Pap Smear Sensitivity Scenario."

All screening modalities were assumed to have equivalent positive predictive values. This was reasonable because the cytologic diagnosis is based on manual review of the slide, and it is likely that the pathologist will call the positive slides in the same manner.[5]

Table 1. Intervention Costs (1997 Dollars)*

Intervention	Reference Case or Discount Rate†	Medicare Value‡	Comments
Revisit cost[20]	$37.00	$25.00	CPT 99212 median reimbursement
Conventional Pap smear with a 10% rescreening rate	$9.75		$1.50 Preparation $7.50 Screening $0.75 Manual rescreening
AutoPap QC 300 rescreening device	$14.75		$1.50 Preparation $7.50 Screening $5.00 Auto rescreening $0.75 Manual rescreening (10%)
AutoPap Primary Screening System	$13.26		$1.50 Preparation $5.00 Auto prescreening $5.63 Screening (75%) $1.13 Manual rescreening (15%)
ThinPrep Pap Test	$19.50		$1.50 Preparation $7.50 Screening $0.75 Manual rescreening $9.75 Disposable
Colposcopy[20]	$362	$169	CPTs 57454 and 88305
LSIL treatment[20]	$185	$111	CPT 57511
HSIL treatment[20]	$796	$399	CPTs 57522 and 88307
Treatment costs for cervical cancer[5]	$18,880	$9440	Approximate mean charges with hysterectomy as the principal procedure + radiation therapy
Costs for dying of cervical cancer[5]	$30,363	$15,182	
Yearly costs for cancer survivors[21]	$ 1000	$500	
Survivor discount rate	3%		
Monetary discount rate	3%		

CPT = *Current Procedural Terminology* codes; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion.
*Device costs are based on manufacturer's quoted prices. Costs for dying and ongoing treatment of cervical cancer are based on a weighted average of the costs by stage at diagnosis.
†Base case values for CPT-4 codes are median values for charges to indemnity insurers.
‡Medicare costs for CPT-4 codes are the national average Medicare allotments.

Outcome Measures

The model produced results in terms of life-years saved with the newer technologies versus conventional Pap smear screening with 10% rescreening. The number of cervical cancer cases and deaths in the unscreened cohort were predicted from the SEER data for incidence[1] and the age-specific rate ratio.[17] The costs in 1997 dollars of a particular screening program were calculated based on the costs shown in Table 1. Medicare reimbursement levels (also shown in Table 1) were used in a separate analysis.

Table 2. Effectiveness of Different Screening Methods

Parameter	Base Case (%)			
	Conventional Screening	AutoPap QC 300 Rescreening Device	AutoPap Primary Screening System	ThinPrep Pap Test
Preparation error[23]	40	40	40	13.3
LSIL sensitivity	84	84	91	84
Overall LSIL sensitivity[2,3]	50.4	55.3	55.2	75.0
HSIL sensitivity	92.0	80	98.5	92.0
Overall HSIL sensitivity[2,3]	55.2	62.3	59.2	82.2
Positive predictive value	90.0	90.0	90.0	90.0
Slides returned	NA	10.0[24]	75.0[25]	NA
ASCUS[25]	9	9	9	7
	High Conventional Pap Smear Sensitivity Scenario (%)			
Preparation error	15.0	15.0	15.0	5.0
LSIL sensitivity	94.0	91.0	60.0	94.0
Overall LSIL sensitivity	80.4	78.4	82.8	90.2
HSIL sensitivity	97.0	98.5	80.0	97.0
Overall HSIL sensitivity	82.9	83.9	86.4	93.1

ASCUS = atypical cells of unknown significance; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; NA = not applicable.

Table 3. Number of Cervical Cancers in a Hypothetical Cohort of 100,000 20-Year-Old Women Until Age 65 for a Selection of Different Screening Methods and Intervals*

Screening Method	No. of Cancers at Interval				
	1 Year	2 Years	3 Years	5 Years	10 Years
Conventional Pap smear	104	252	386	646	1211
AutoPap QC 300 rescreening device	90	226	349	588	1121
AutoPap Primary Screening System	90	226	349	588	1119
ThinPrep Pap Test	38	130	215	377	744

*In the absence of screening there would be 2147 cancers in the cohort.

Table 4. Incremental Cost Effectiveness of Different Screening Methods and Intervals of Cervical Cancer Screening for Women Age 20-65 Years*

Screening Method	Screening Interval (y)	Average Cost ($)*	Life-Days Saved*	Incremental Cost ($)*	Incremental Life-Days*	Cost/Life-Year Saved ($)
Conventional Pap	10	556	3.5			
AutoPap Primary Screening System	10	562	3.8	7	0.292	8579
AutoPap QC 300 rescreening device	10	566	3.8	3	-0.005	Dominated
ThinPrep Pap Test	10	569	5.1	3	1.286	807
Conventional Pap	5	629	5.6	61	0.560	39,545
AutoPap Primary Screening System	5	640	5.9	10	0.249	14,909
AutoPap QC 300 rescreening device	5	646	5.9	6	-0.001	Dominated
ThinPrep Pap Test	5	647	6.9	2	0.979	703
Conventional Pap	3	699	6.8	52	-0.022	Dominated
AutoPap Primary Screening System	3	714	7.0	15	0.188	29,125
AutoPap QC 300 rescreening device	3	724	7.0	10	0.001	4,439,071
ThinPrep Pap Test	3	729	7.7	5	0.719	2454
Conventional Pap	2	782	7.5	53	-0.194	Dominated
AutoPap Primary Screening System	2	805	7.7	23	0.144	58,194
AutoPap QC 300 rescreening device	2	820	7.7	14	0.001	5,200,521
ThinPrep Pap Test	2	836	8.2	16	0.542	10,744
Conventional Pap	1	1062	8.4	226	0.156	527,520
AutoPap Primary Screening System	1	1112	8.5	50	0.085	215,884
AutoPap QC 300 rescreening device	1	1140	8.5	28	0.001	15,529,711
ThinPrep Pap Test	1	1191	8.8	51	0.307	60,183

*Per-capita calculations were based on an average of 96,372 women surviving each year during the course of screening. Costs were discounted 3% per year.
"Dominated" means that it costs more and produces fewer life-years than other options.

Both benefits (life-years saved) and costs (dollars) were discounted on an annual basis. We used a 3% per year discount rate for both costs and benefits. The model also reported the undiscounted average yearly incidence of cervical cancer that would occur in the cohort during the course of screening.

Comparison with Reported Incidence

This model has the ability to predict the average number of cancers per year throughout the screening regimen, as well as the lifetime risk of being diagnosed with cervical cancer. Using the results of the model at different screening intervals combined with known utilization metrics for cervical cancer screening, it was possible to predict the effects of new technologies on the cervical cancer incidence rate with no change in screening utilization. These results can be compared with reported incidence rates. According to an abstract of the 1992 National Health Interview Survey,[26] 70.5% of all women between 20 and 65 years of age were screened in the last 3 years and 7.5% had never been

screened. This leaves 22% of women in the 20- to 65-year age range who received suboptimal screening. It was assumed that women who received screening in the last 3 years (70.5%) were divided among annually, biannually, and triannually. Using the 90% composite participation rate at one of the authors' (BMB) managed healthcare plans (Harvard Vanguard Medical Associates, Department of Pathology and Laboratory Medicine, 1996, unpublished data), the known frequency of screening for the participating members was used to project the screening frequency in a compliant population. As a result, we assumed that 34.5% of the model population was screened annually, 25.3% was screened biannually, and 10.7% was screened triannually. Women who have ever been screened were assumed to be underserved and split evenly (11% each) between a 5-year screening interval and a 10-year screening interval for lack of better published information. This leaves 7.5% who never received screening.

··· RESULTS ···

The model predicted there would be 2147 (an average of 47 cancers per year) cervical cancers in an unscreened cohort, causing 626 women to die and lose 2384 discounted life-years. If there were no screening program, the system would spend $31 million (discounted) over the 46-year time frame of the model caring for cervical cancer patients. The conventional Pap smear would reduce the incidence of cervical cancer to 104 cases, 386 cases, and 646 cases for 1-year, 3-year, and 5-year intervals, respectively, over the course of the screening regimen. New technologies that have a marginal improvement in sensitivity of 7% to 12% (AutoPap QC 300 rescreening device and AutoPap Primary Screening System) would reduce the incidence of cervical cancer by 9% to 14% compared with the conventional Pap smear, whereas new technologies that improve sensitivity by 49% (ThinPrep Pap Test) would reduce cervical cancer by 42% to 63%. Table 3 shows the number of cancers in the 100,000-women cohort over the course of the screening program (ages 20-65 years) if they were screened with the different modalities at a variety of screening intervals.

Table 4 shows the incremental cost per life-year saved for each of the cervical cancer screening strategies and frequencies. The strategies are rank-ordered from least to most expensive, and the cost-effectiveness ratios are presented in terms of the next-least-expensive approach.

Table 5 shows the cost effectiveness of each technology compared with the conventional Pap smear at the same screening frequencies for the entire screened cohort. This table can be used to determine the relative cost effectiveness of switching from conventional Pap smears to one of the new technologies. Table 5 shows clearly that the significant improvement in test sensitivity provided by the ThinPrep Pap Test makes it the most cost-effective new technology despite its higher per-test cost. Because the AutoPap technologies have not been approved for use with ThinPrep Pap Test slides, all of the modalities are compared directly with the conventional methodology instead of to each other.

Although there is little room for improvement in a fully compliant, annually screened population, it can be seen that use of new technologies has the potential to significantly reduce the number of cancers. There is limited evidence, however, that it will be feasible to screen all women annually,[27-29] and annual screening may not be the relevant interval with which to evaluate new technologies.

Effect of Screening Interval

The model was run with a variety of screening intervals (1, 2, 3, 5, and 10 years). Table 3 shows the number of cancers for each of the modalities modeled at different screening intervals. The cost effectiveness of the new technologies compared with conventional Pap smears with 10% rescreening is shown in Figure 2.

All the new technologies become more cost effective than conventional screening as the screening interval is increased (Table 5). The ThinPrep Pap Test has a cost-effectiveness ratio of less than $50,000 per life-year saved at intervals longer than 1 year, and the other new technologies are cost effective at screening intervals longer than 3 years.

Validation of Results

The model results were compared with the AHCPR results[3] and the recent report by Brown and Garber.[5] The results of this comparison are shown in Table 6. The current model's results are fairly close to the AHCPR results with a slightly lower incidence overall and a higher ratio of cancer incidence to mortality. Both the current and AHCPR results differ from the Brown and Garber results, especially in terms of the effect of screening interval.

A more robust method of validation is to determine how closely the model predicts the known

incidence of cervical cancer. Compliance with screening and follow-up recommendations is not complete. Data estimating Pap smear utilization from the National Hospital Interview Survey[12] and the composite participation rate at one of the authors' (BMB) managed healthcare plans (Harvard Vanguard Medical Associates, Department of Pathology and Laboratory Medicine, 1996, unpublished data) were combined in a weighted manner with the results of the different screening intervals to estimate the impact of actual utilization rates on cancer incidence. In addition, the compliance with colposcopy recommendations is not perfect; therefore, an estimate of 20% noncompliance with colposcopy recommendations was used for this analysis.[30,31] This analysis for conventional screening yielded an average of 13.2 cancers per year, which is comparable to the number predicted from the SEER data of 12.8 cancers per year in the screened cohort.[1] The lifetime risk of a 20-year-old woman entering the screening cohort was calculated to be 0.71%, which is comparable to the 0.79% risk reported by SEER.[1] Table 7 shows the results of this comparison for the screening modalities studied. When utilizing the ThinPrep Pap test results, the model predicted that there would be 9.5 cancers

Table 5. Incremental Cost per Life-Year Saved for Different Cervical Cancer Screening Methods for a Cohort of 100,000 20-Year-Old Women Until Age 65

Screening Method*	Total Cost ($000,000)	Incremental Cost ($000,000)	Years of Life Gained	Cost/Life-Year Saved ($)
		10-Year Screening Interval		
Conventional Pap (compared with no Pap)	53.5	22.2	922	24,096
AutoPap QC 300 rescreening device	54.5	1.0	76	13,063
AutoPap Primary Screening System	54.2	0.7	77	8579
ThinPrep Pap Test	54.8	1.3	415	3045
		5-Year Screening Interval		
Conventional Pap (compared with no Pap)	60.7	29.3	1485	19,748
AutoPap QC 300 rescreening device	62.2	1.6	66	23,862
AutoPap Primary Screening System	61.6	1.0	66	14,909
ThinPrep Pap Test	62.4	1.7	324	5392
		3-Year Screening Interval		
Conventional Pap (compared with no Pap)	67.4	36.1	1803	20,006
AutoPap QC 300 rescreening device	69.8	2.4	50	48,077
AutoPap Primary Screening System	68.9	1.4	50	29,125
ThinPrep Pap Test	70.3	2.9	240	11,952
		2-Year Screening Interval		
Conventional Pap (compared with no Pap)	75.4	44.1	1992	22,130
AutoPap QC 300 rescreening device	79.0	3.6	38	94,194
AutoPap Primary Screening System	777.6	2.2	38	58,194
ThinPrep Pap Test	80.6	5.2	181	28,393
		1-Year Screening Interval		
Conventional Pap (compared with no Pap)	102.3	71.0	2215	32,057
AutoPap QC 300 rescreening device	109.9	7.6	23	336,017
AutoPap Primary Screening System	107.1	4.8	22	215,884
ThinPrep Pap Test	114.3	12.4	104	120,129

*All methodologies are compared with conventional Pap smears with the same screening frequencies. The various screening methods are compared individually because the new methodologies are not approved for use in combination.

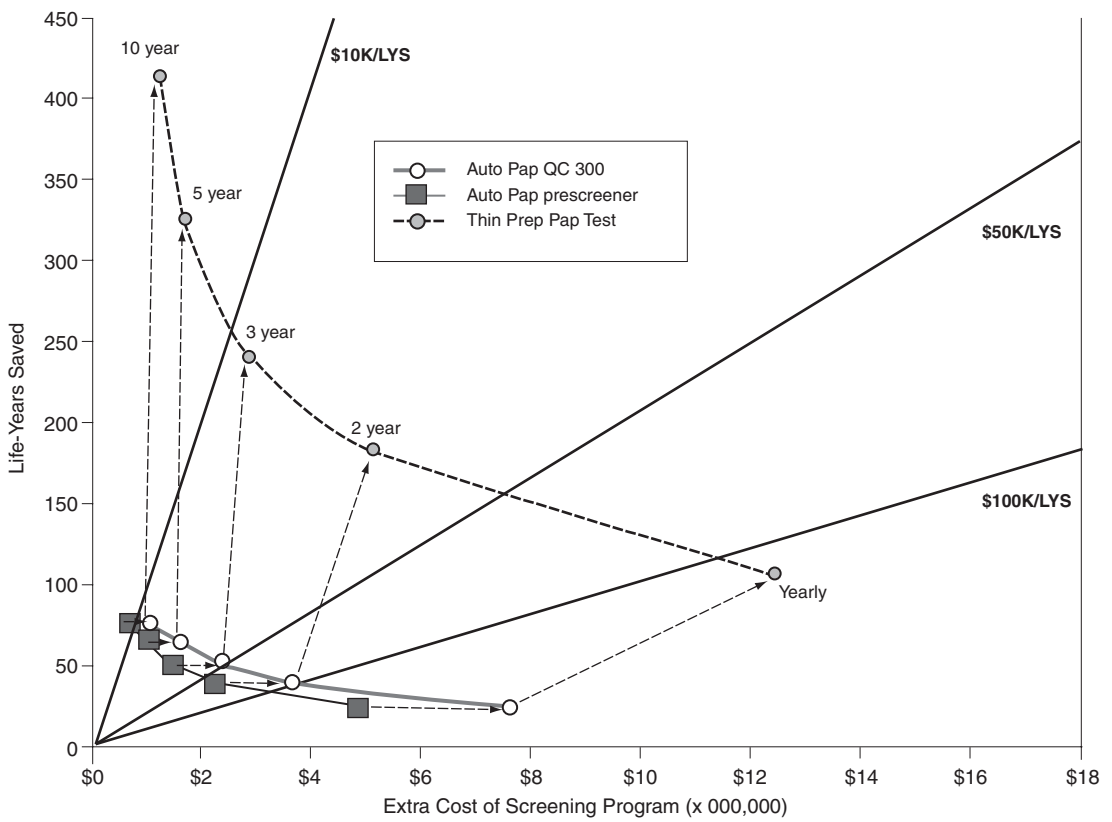
per year and a 0.51% risk of cervical cancer for a 20-year-old woman.

The Agency for Health Care Policy and Research also utilized this method to validate their results for the conventional Pap smear. That model, however, was run "varying the proportion of the cohort who received no and Pap smears every 5, 3, 2, and 1 years," attempting to match cervical cancer diagnosis and mortality to the SEER data.[3] In the approach presented here, published data for Pap smear utilization were used to determine whether the modeled results closely match the SEER data. In addition, the AHCPR did not report taking the further step of determining the effect on these results of utilizing the new higher-sensitivity technologies.

Sensitivity Analyses

The model was run with different parameters to show that it would produce a similar rank order of the methods when the test sensitivity and intervention costs were varied. One analysis utilized half the overall false-negative rate for CIN, resulting in a combined sensitivity of 80%. The other analysis utilized Medicare reimbursement rates (low cost) for the follow-up and treatment procedures (Table 1). In both cases, the benefits accrued to the various new technologies were muted, but the relative positions of the new strategies remained the same. These effects are shown graphically in the cost-effectiveness charts in Figures 3 and 4.

Figure 2. Cervical Cancer Screening Program Cost Effectiveness by Screening Interval and Screening Modality Compared with Conventional Pap Smear—Base Case



LYS = life-years saved.
Strategies that are above (save more life-years) and to the left (cost less) of other strategies are considered to be dominant in cost effectiveness. Arrows represent relative cost effectiveness between technologies at the same screening frequency.

··· DISCUSSION ···

The model reaffirms the fact that there is little risk of cervical cancer in a population of annually screened women. As the general population moves away from this ideal situation, however, the cervical cancer risks dramatically increase. As shown in Table 3, a woman who is conventionally screened every 5 years has 6 times the risk of being diagnosed with cancer as a woman screened yearly. For a woman screened every 10 years, the risk is magnified 12-fold compared with an annually screened woman. In practice, the majority of women are not screened annually, and the model shows the dramatic improvement in outcomes from tests that have significantly improved test sensitivity. Additionally, this improvement in cancer incidence and deaths can be realized within the constraints of reasonable cost effectiveness. It is critical to create a modeling technique that can utilize actual compliance patterns to gauge the impact of new technologies in a real-world setting.

Using the average number of cancers per year combined with known utilization metrics for cervical cancer screening, it is possible to predict the effects of

Table 6. Comparison of Previously Published Models and Current Model with Respect to Reduction of Cumulative Lifetime Incidence of Health Effects per 100,000 Women Screened for Cervical Cancer

		Brown and Garber[5]*	AHCPR†		Current Model‡	
Screening Interval	Health Effect	80%	Base (51%)	80%	Base (50.4%)	80%
Annual	Cancers	200	109	33	115	38
	Deaths	60	20.9	5.8	37	13
Biannual	Cancers	240	305	132	270	123
	Deaths	80	65	25.2	85	39
Triannual	Cancers	280	506	246	409	200
	Deaths	90	115.7	49.8	130	63

AHCPR = Agency for Health Care Policy and Research.
*Health effects were calculated for the lifetime of women starting at age 20 years. No data for base sensitivity are available. Women were screened between the ages of 20 and 65 years.
†Health effects were calculated for women between the ages of 15 and 85 years. Women were screened between the ages of 15 and 85 years.
‡Health effects were calculated for women between the ages of 20 and 80 years. Women were screened between the ages of 20 and 65 years.

Table 7. Average Yearly Incidence of Cervical Cancer in the General Population Age 20-65 Years, Estimated Lifetime Risk of Being Diagnosed with Cervical Cancer, and Cost per Life-Year Saved Given Current Cervical Cancer Screening Utilization Rates (per 100,000 Women)*

	Full Population			Regularly Screened Population (At Least Every 3 Years)	
Screening Modality	Lifetime Risk for 20-Year-Old	Cancers/Year/ 100,000 Women	Cost/Life-Year Saved ($)†	Cancers/Year/ 100,000 Women	Cost/Life-Year Saved ($)
Conventional Pap smear with a 10% rescreening rate	0.71%	13.2	NA	6.0	NA
AutoPap QC 300 rescreening device	0.67%	12.4	125,501	5.5	172,146
AutoPap Primary Screening System	0.67%	12.4	79,338	5.5	108,883
ThinPrep Pap Test	0.51%	9.5	41,464	3.4	57,531

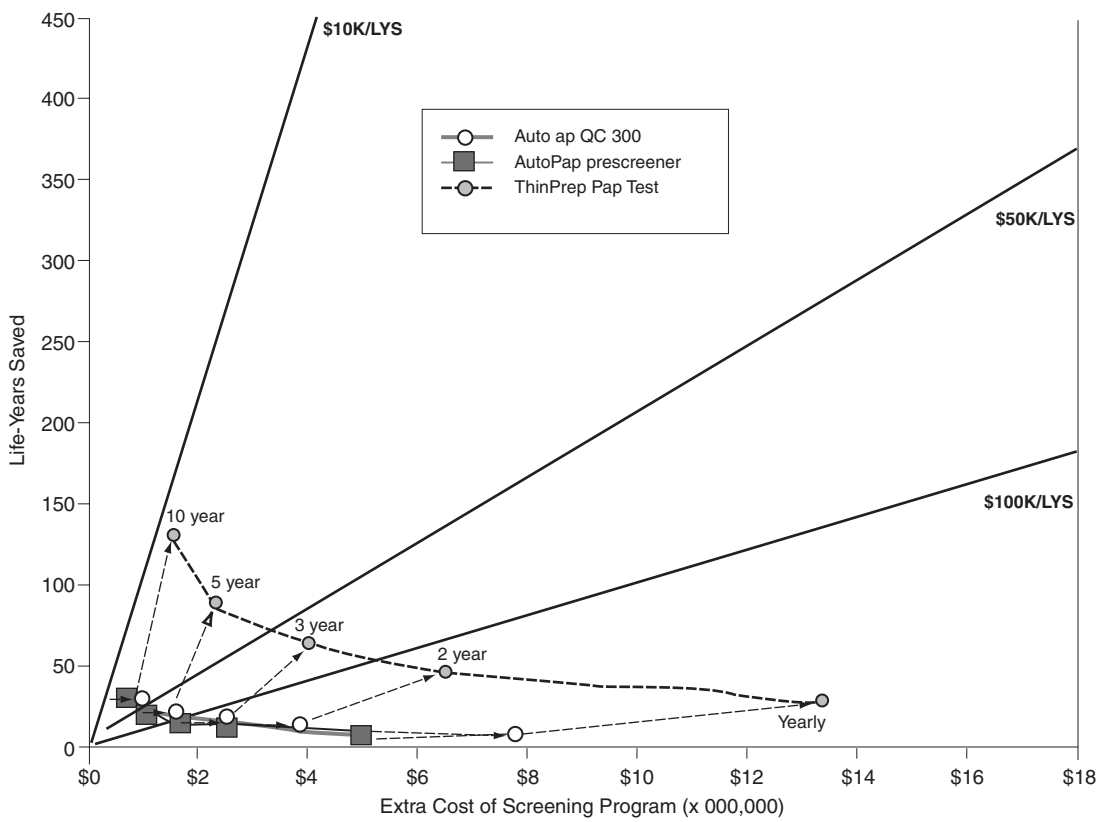
NA = not applicable.
*Current utilization rates are based on National Hospital Interview Survey data for screening participation of women ages 20-65 years.[12]
†Cost per life-year saved was calculated using a conventional Pap smear with a 10% rescreening rate as the basis of comparison.
SEER data would predict 12.8 cancers per year and a 0.79% lifetime risk of being diagnosed with cervical cancer.[1]

new technologies on the cervical cancer incidence rate with no change in screening utilization. Table 7 shows the results of the model for these utilization numbers. This approach was used to validate the results of the model by comparing the SEER incidence of cancer (12.8 cases per 100,000 women per year) to the model's predicted incidence of cancer (13.2 cases per 100,000 women per year).

As shown in Table 7, the methods for automatically choosing slides for (re)screening could reduce the incidence of cancers from 13.2/100,000 per year to 12.4/100,000 (6% reduction), whereas utilizing a method that reduces preparation errors would reduce the incidence to 9.5/100,000 cancers per year (28% reduction) in the entire population. The ThinPrep Pap Test had the lowest cost-effectiveness ratio of $41,464 per life-year saved, compared with the AutoPap Primary Screening System at $79,338 per life-year saved and the AutoPap QC 300 rescreener at $125,501 per life-year saved.

In a Health Employer Data and Information Set-compliant managed care population (85% screened at least every 2 years and the other 15% screened every 3 years),[32] based on actual utilization rates at one of the authors' (BMB) managed care plans (Harvard Vanguard Medical Associates, Department of Pathology and Laboratory Medicine, 1996, unpublished data), these same technological approaches offer an 8.3% and a 43% reduction in yearly cancers, respectively. In the managed care setting, only the ThinPrep Pap Test had a cost-effectiveness ratio under $100,000 per life-year saved at $57,531 per life-year saved. The AutoPap Primary Screening System had a cost-effectiveness ratio of

Figure 3. Cervical Cancer Screening Program Cost Effectiveness by Screening Interval and Screening Modality Compared with Conventional Pap Smear—High Sensitivity of Conventional Screening



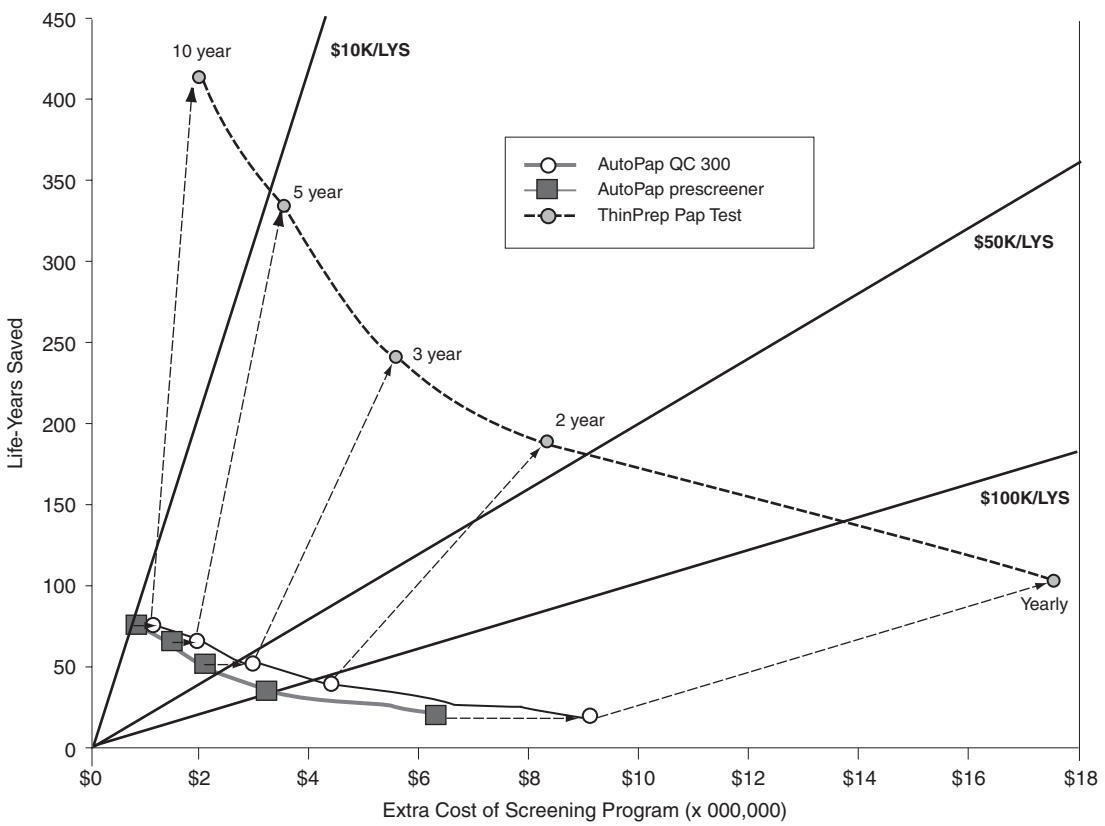
LYS = life-years saved.
Strategies that are above (save more life-years) and to the left (cost less) of other strategies are considered to be dominant in cost effectiveness. Arrows represent relative cost effectiveness between technologies at the same screening frequency.

$108,883 per life-year saved, and the AutoPap 300 rescreener had a cost-effectiveness ratio of $172,146 per life-year saved. These findings show that, considering current program utilization in a managed care setting, using a test that significantly increases the test sensitivity can improve cervical cancer outcomes at reasonable cost-effectiveness ratios.

A recent report by Brown and Garber found that new technologies had significantly worse cost-effectiveness ratios than those found by this new model.[5] One factor contributing to the difference in these new results is the choice of the test sensitivity of the conventional Pap smear. When using the same sensitivity used by Brown and Garber (80%), however, our model produced health effect results different from those reported by Brown and Garber for conventional screening (Table 6). Nonetheless, the currently reported results closely match the AHCPR results at both an 80% test sensitivity and the known base sensitivity of ~51% (Table 6).[3] The modeled base sensitivity of 50.4% more closely predicts the actual cervical cancer incidence.

One issue not addressed by the base sensitivity model is the impact of slides designated as SBLB. These slides represent a clinical dilemma, as the primary care physician cannot be sure that the Pap smear results are reliable. There is evidence that the ThinPrep Pap Test reduces the incidence of SBLB slides by up to 50% and as such may represent an improvement in effectiveness of the cervical screening program.[33] If it is assumed that all women with SBLB smears return for a second Pap smear in the

Figure 4. Cervical Cancer Screening Program Cost Effectiveness by Screening Interval and Screening Modality Compared with Conventional Pap Smear—Low-Cost, Medicare Assumptions



LYS = life-years saved.
Strategies that are above (save more life-years) and to the left (cost less) of other strategies are considered to be dominant in cost effectiveness. Arrows represent relative cost effectiveness between technologies at the same screening frequency.

same year, the yearly cost-effectiveness ratio for the ThinPrep Pap Test is reduced to an incremental $65,664 per life-year saved compared with yearly conventional Pap smears. Because there is no evidence that 100% of women with SBLB slides actually return for a repeat Pap smear, it is unlikely that the actual cost-effectiveness ratio is this low. The ability of the ThinPrep Pap Test to reduce the incidence of SBLB slides, however, could potentially lower the cost-effectiveness ratio for this test, depending on how many women actually are retested.

One problem in implementing these models is the lack of consistently presented information about the efficacy of the new screening technologies. In particular, information is required regarding the sensitivity of the rescreening devices to slides with abnormal cells that were missed by the initial screening cytotechnologist. Much of the data in the literature about the efficacy of the rescreening systems do not separate the performance of the automated rescreening device from the accuracy of the cytotechnologist actually performing the rescreening. Data on technical sensitivity, technical specificity, and prevalence of disease in the study population are the minimum essential data elements for meaningful measures of performance. An intersociety working group took the lead in defining these parameters,[34] but studies rigorously adhering to the guidelines have yet to be completed. For this reason, studies presented by the various companies in their respective FDA filings form the basis of the device's modeled effectiveness.

Another difficulty is a lack of hard information regarding the incidence of ASCUS and how these cases are actually followed in practice. For this reason, the simplifying assumption was made that women with ASCUS smears received a single repeat smear in the same year as the initial ASCUS result, and there was a 33% chance that the repeat smear resulted in a diagnostic colposcopy. Therefore, our model may understate the cost of an ASCUS Pap smear, and a more in-depth analysis of the follow-up protocols for ASCUS is warranted.

··· CONCLUSION ···

Historically the sensitivity of the conventional Pap smear has been overstated.[2,3] New predictive models now have validated the lower sensitivity of the Pap smear by predicting the known cancer incidence in a population at normal risk. Nonetheless, it is currently accepted that a population compliant with Pap smear screening recommendations would have a significantly lower rate of cervical cancer than is currently reported. As noted by O'Leary et al, 75% of all cervical cancers occur in women who have received a suboptimal screening regimen.[8] This point is further solidified by the Healthy People 2000 program: reducing the mortality due to cervical cancer by 50% is a portion of its 16th priority and increasing the percentage of women receiving a Pap smear in the last 3 years to 85% is a stated goal in its 21st priority.[35]

Nonetheless, 25% of cancers still occur in women who are regularly screened (at least every 3 years), possibly in a managed care setting. Based on the predictive approach utilized in this model, 33% (4.3/13.2) of the cancers would occur in a regularly screened population. This report shows that a significant impact on these preventable negative outcomes can be achieved with the use of a technique that increases Pap smear sensitivity at a reasonable cost.

This raises the question of whether the new technologies can be used in conjunction with increasing utilization to achieve the national cancer mortality goal. As can be seen from the average numbers of cancers in Table 7, the use of the ThinPrep Pap Test would reduce the incidence of cervical cancer by 28% (3.7/13.2) using current utilization rates for the Pap smear in the general population. In a compliant population (screening at least every 3 years), new technology has the potential to reduce the incidence of cervical cancer by 43% (2.6/6.0). This model shows that the effectiveness of the cervical cancer screening program depends on the test sensitivity of the screening technology used. In fact, if the test sensitivity is increased by 50% with a new test, the new test can be deployed quite cost effectively in spite of increased per-test cost. This does not obviate the need to increase utilization of the Pap smear. In fact, more complete compliance with Pap testing coupled with more sensitive technologies would have an even greater effect on mortality from cervical cancer.

There is not much information regarding the costs of programs that would be effective at increasing Pap smear compliance. In fact, some reports show that many forms of utilization-enhancing programs have little or no effect.[27,28] Therefore, it is difficult to directly compare the cost effectiveness of new technologies with the cost effectiveness of programs to increase Pap smear utilization.

Several new analyses would be interesting to perform. One is the impact of new technologies in areas of the world that are currently underserved with cervical screening programs. For instance, what would be the most effective combination of technologies and screening intervals for establishing a

screening program in a Third World setting? Another analysis would take into account quality-of-life issues as a means for allowing managed care organizations to make coverage decisions based on the preferences of the women being screened.

This model is capable of predicting the outcomes and costs associated with different compliance levels as well as different technologies and shows the potential gains that may be achieved by improving compliance. As we appear to be reaching the limits of compliance, however, the widespread adoption of a technique that dramatically improves test sensitivity may be the most realistic means for achieving the goal of further reducing cervical cancer incidence and mortality in a cost-effective manner.

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