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Setting the Target for a Better Cervical Screening Test: Characteristics of a Cost-Effective Test for Cervical Neoplasia Screening

EVAN R. MYERS, MD, MPH, DOUGLAS C. MCCRORY, MD, MHSC, SUJHA SUBRAMANIAN, PhD, NANCY MCCALL, PhD, KAVITA NANDA, MD, MHS, SANTANU DATTA, MBA, MS, AND DAVID B. MATCHAR, MD

Objective: **To determine the potential effects on costs and outcomes of changes in sensitivity and specificity with new screening methods for cervical cancer.**

Methods: **Using a Markov model of the natural history of cervical cancer, we estimated the effects of sensitivity, specificity, and screening frequency on cost-effectiveness. Our estimates of conventional Papanicolaou test sensitivity of 51% and specificity of 97% were obtained from a meta-analysis. We estimated the effect of reducing false-negative rates from 40–90% and increasing false-positive rates by up to 20%, independently and jointly. We varied the marginal cost of improving sensitivity from $0 to $15.**

Results: **When specificity was held constant, increasing sensitivity of the Papanicolaou test increased life expectancy and costs. When sensitivity was held constant, decreasing specificity of the Papanicolaou test increased costs, an effect that was more dramatic at more frequent intervals. Decreased specificity had a substantial effect on cost-effectiveness estimates of improved Papanicolaou test sensitivity. Most of those effects are related to the cost of evaluation and treatment of low-grade lesions.**

Conclusion: **Policies or technologies that increased sensitivity of cervical cytologic screening increased overall costs, even if the cost of the technology was identical to that of conventional Papanicolaou smears. These effects appear to be caused by relatively high prevalence of low-grade lesions and are magnified at frequent screening intervals. Efficient cervical cancer screening requires methods with greater ability to detect lesions that are most likely to become cancerous. (Obstet Gynecol 2000;96:645–52. © 2000 by The American College of Obstetricians and Gynecologists.)**

From the Department of Obstetrics and Gynecology, Center for Clinical Health Policy Research–Evidence-Based Practice Center, and Division of General Internal Medicine, Duke University Health System and Durham Veterans Affairs Medical Center, Durham, North Carolina; and Health Economics Research, Inc., Boston, Massachusetts.

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Carcinoma of the cervix is one of the most common malignant conditions in women in many parts of the

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world. Papanicolaou smears detect preinvasive and early invasive disease and have led to significant reductions in its incidence and associated mortality in many countries.[1] In the United States, the incidence of and mortality rate associated with cervical cancer have declined steadily; National Cancer Institute Surveillance, Epidemiology, and End Results registry data show a 43% decrease in incidence and a 46% decrease in mortality from 1973 to 1995.[2] No such reductions occurred in countries in which cytologic screening is not widely available.[3]

In the United States and other countries in which screening is widely available, at least 40% of cases of cervical cancer occur in the 5–15% of women who have never been screened.[4–6] Despite evidence that many cases are attributable to inadequate screening or inadequate follow-up of abnormal results, attention has been increased toward reducing false-negative results in women who are screened.

Several adjunctive technologies intended to reduce false-negative results of conventional smears have been approved by the U.S. Food and Drug Administration. Recent evaluations by our group[7] and the Blue Cross/Blue Shield Technology Evaluation Center[8] found that the cost-effectiveness of adjunctive technologies is directly related to frequency of screening. However, limitations in the extant evidence on sensitivity, specificity, and cost of new technologies do not permit reliable estimates of the cost-effectiveness of individual new tests. Therefore, we applied a comprehensive model of cervical cancer to identify circumstances in which new technologies could be cost-effective.

Methods

The foundation for this work was our comprehensive model of the natural history of cervical cancer, which incorporates published values for probabilities related to the natural history of cervical cancer and outcomes of diagnoses and treatment for cervical dysplasia and cancer. The structure, parameter estimates, source data, and predictions of the natural history model are described in detail elsewhere[7,9]; additional details are available from the authors on request. We created a Markov state-transition model with discrete 1-year cycle lengths that simulates a cohort of women 15–85 years of age. The model is based on the assumption that all cervical cancer arises from infection with human papillomavirus (HPV), which progresses sequentially from low-grade through high-grade squamous intraepithelial lesions (SIL) to invasive cervical cancer of various stages. The model accounts for a proportion of HPV infections progressing directly to high-grade SIL. Infection with HPV, low-grade SIL, and high-grade SIL might progress or regress at age-dependent rates. During simulation, women might also die from causes unrelated to cervical cancer or have hysterectomies for reasons other than cervical cancer or its precursors, thus removing them from the at-risk pool. The model predicts a peak incidence of cervical cancer at 47 years of age of 81 of 100,000 women (uncorrected for hysterectomy), and results in an age-specific incidence curve similar to that in many unscreened populations.[1,10] Predicted age-specific prevalence of HPV, low-grade SIL, and high-grade SIL are also consistent with reported cross-sectional data. The natural history model was adapted to incorporate screening strategies by allowing the possibility of screening during each 1-year Markov cycle.

We used a "health system" perspective that considered the direct medical costs associated with the screening, diagnosis, and treatment of low- and high-grade SIL and cervical cancer. We did not include direct nonmedical costs (eg, cost of transportation to screening site).

Our measure of the comparative value of alternative testing strategies was the incremental cost per life-year saved, calculated by dividing the difference in predicted costs between two strategies by the difference in average life expectancy predicted for the strategies.

During each cycle of the Markov model, women were given screening procedures with some degree of sensitivity, specificity, and cost. Adjunctive technologies can be characterized by their reduction in rate of false-negative results (equivalent to the relative rate of true-positive results) compared with that of conventional tests.[7] In that analysis, we model the overall test characteristics of a single generic technology (as a single test or in rescreening strategies) and its marginal cost compared with conventional Papanicolaou smears.

Abnormal cytologic results include atypical squamous cells of undetermined significance (ASCUS), low-grade SIL, high-grade SIL, or cancer. We assumed that any cytologic result of high-grade SIL or cancer would mean immediate referral for colposcopy, with biopsy if warranted. We further assumed that endocervical curettage was done routinely as part of colposcopic evaluations. Because not every woman will have endocervical curettage, that assumption might overestimate sensitivity and the average cost of colposcopy. We also assumed that a colposcopic or histologic diagnosis that is significantly less advanced than the cytologic result would lead to further diagnostic testing. For example, a biopsy result of low-grade SIL (or cervical intraepithelial neoplasia [CIN]) in the setting of a cytologic diagnosis of cancer or a biopsy result of normal with cytologic high-grade SIL would result in cone biopsy or

Table 1. Probabilities and Rates for Screening Model

Parameter	Base case	Range	Reference
Sensitivity* of conventional test	51%	51–88%	7,15–19
Specificity* of conventional test	97%	95–98%	7,15–19
Sensitivity of colposcopy with biopsy	100%		Assumption
Sensitivity of cytology and pelvic examination for stage II–IV cervical cancer	100%		Assumption
Proportion of women with abnormal results receiving appropriate follow-up	100%		Assumption
Increase in sensitivity of new test	None assigned	40–90%	8,20–26
Decrease in specificity of new test	0%	0–20%	Assumption

* Cytologic threshold of atypical squamous cells of undetermined significance or worse and histologic diagnosis of low-grade squamous intraepithelial lesion or worse.

loop electrosurgical excision procedure after excluding disease elsewhere in the lower genital tract.[11]

In the base case, we assumed that all women with low-grade SIL or higher would receive colposcopies, whereas those with ASCUS would receive repeat smears within 6 months, followed by colposcopies if results were abnormal. Because that strategy depends on a test of high sensitivity (because colposcopy depends on persistence of abnormality), we used it in the base case. Although more conservative management of low-grade SIL (such as observation) is being used increasingly, we also assumed that all low-grade SIL would be treated, primarily to be consistent with other models.

We assumed that women who survived 5 years or more were no longer at risk of recurrence, as have other models,[12–14] and that mortality associated with complications of therapy was included in cancer survival probabilities. Because some uncertainty exists in the literature about whether treatment of SIL results in total eradication of HPV infection, we created a "diagnosed HPV" state to represent women treated for SIL and allowed them to have a reduced progression rate. We assumed that the probability of progression was 5% of the age-specific progression rates, equivalent to a 95% cure rate for SIL treatment in other commonly cited models.[12–14] In the model, we assumed that adherence to appropriate management protocols would be perfect. Imperfect adherence increases the cost-effectiveness ratio by decreasing the effectiveness of the intervention.

Sources and values for model parameters are described below and are shown in Table 1, along with plausible ranges. Our sensitivity and specificity estimates for conventional tests were based on a meta-analysis,[7,15] that confirmed results of a previous meta-analysis.[16] We used a cytologic threshold of ASCUS as a positive result and a histologic diagnosis of low-grade SIL or higher for true-positive results; estimated sensitivity is 51% and specificity is 97%. We assumed that the sensitivity and specificity of conventional smears for low-grade lesions were identical to those for high-grade lesions and cancer, despite evidence that suggested that sensitivity of conventional Papanicolaou smears improves with increased severity of lesions.[15,16]

We assumed that sensitivity of combined cytologic tests, visual examination of the vagina and cervix, and bimanual examination for stages II to IV was 100%. Because cancers at those stages will by definition involve the vagina or parametrial tissues, failure to detect an abnormality cannot be attributed to test characteristics of the Papanicolaou smear. There is no reason to predict that sensitivity of the combined cytologic test and pelvic examination would differ at those stages using conventional or new technologies.

We varied the reduction in the rate of false-negative results (equivalent to an increase in sensitivity) from 40–90%, which incorporates the most effective reported range of improvement in sensitivity for currently approved adjunctive technologies. Without substantial data on relative specificity of new technologies compared with conventional tests, we assumed that the specificity of the hypothetical new test would be equivalent to that of the conventional test and decreased it to 75% of the value of the conventional test in sensitivity analysis. We estimated the marginal cost of the new technology compared with conventional Papanicolaou smears to range from $0 to $15.

For each histologic state, we calculated the proportion of all abnormal results represented by each possible cytologic diagnosis by using published data from the College of American Pathologists.[27] Among women with ASCUS or worse on screening tests, some have ASCUS, some have low-grade SIL, some have high-grade SIL, and some have cancer. Those proportions vary depending on the underlying histologic condition. In the model, we combined ASCUS and atypical glandular cells of undetermined significance (AGCUS). The proportion of AGCUS smears with underlying high-grade pathology might be as high as 35%,[28] which improves overall sensitivity for any screening strategy because a cytologic diagnosis of ASCUS will detect a higher proportion of clinically significant lesions. We assumed that those conditional probabilities would be similar for new technologies.

Stage-specific survivals for invasive cancer were derived from data from the Patterns of Care program of

Table 2. Cost Estimates for Model

Parameter	Base case	Range
Screening		
Conventional cytology ($)		
Age 15–64 years	38.68	35.32–43.77
Age 65 years or older	47.73	44.24–56.98
Marginal cost of hypothetical new test compared with conventional cytology ($)	10	0–15
Diagnosis		
Colposcopy only ($)	142.63	81–179
Colposcopy and biopsy ($)	276.57	195–351
Colposcopy, biopsy, and endocervical curettage ($)	375	244–477
Loop electrosurgical excision procedure ($)	564	352–710
Cone biopsy ($)	919	623–1114
Evaluation and treatment		
Low-grade squamous intraepithelial lesion ($)	1728	675–2274
High-grade squamous intraepithelial lesion ($)	3049	1384–4203
Cervical cancer ($)		
Stage I	17,645	9439–21,946
Stage II	27,069	11,734–29,089
Stage III	27,069	11,734–29,089
Stage IV	40,280	12,670–46,509
Terminal care	16,530	10,000–25,000

the American College of Surgeons[29] (and A. Fremgen, personal communication).

Cost estimates of conventional smears and diagnosis and treatment of low-grade SIL, high-grade SIL, and various stages of cervical cancer were estimated by using primary claims and secondary data sources (Table 2). Details were published[7] or are available from the authors on request. A comprehensive approach was used to incorporate costs associated with all medical services provided. For instance, the costs associated with physician and pathology services were included in the total cost of screening for cervical cancer. For diagnosis and treatment, all costs of providing outpatient and inpatient services were estimated. However, societal costs or indirect costs, such as those associated with lost wages or waiting time at the physician's office, were not included.

Separate estimates were made for women 20–64 years of age and those 65 years of age or older (those eligible for Medicare). The costs for the population younger than 65 years of age were estimated from claims data from the MEDSTAT group, whereas Medicare's resource-based relative value system fee schedule, clinical laboratory fee schedule, diagnosis-related group payment rates, and ambulatory surgery center payment rates were used to estimate costs in the older subgroup. Charges and payment information from those sources were converted to reflect costs associated with services provided. Costs were inflated to 1997 dollars.

Estimates based on episodes of care were consistently higher than estimates based on procedure-specific costs (owing to such factors as complications, comorbid conditions, and varying severity of disease within stages); we therefore used the higher estimates. Compared with previous estimates, our cost estimates for conventional screening were substantially lower, and our cost estimates for cervical cancer diagnosis and treatment substantially higher; this is consistent with our goal of favoring more sensitive strategies in the base case. We discounted costs and years of life at 3% annually in the base case and varied the rate from 0% to 5% in sensitivity analysis.[30]

We used one-, two-, and three-way sensitivity analysis of all variables to determine the effects of uncertainty surrounding cost and probability estimates on the model's results. Because few data exist on specificity of new technologies, we examined potential effects of joint effects (ie, decreasing specificity as sensitivity increases) on a hypothetical new technology with a marginal cost of $0 per slide at 1-, 2-, and 3-year screening intervals. We sought to identify the values (thresholds) for sensitivity, specificity, or cost for which a strategy-involving a new technology would be cost-saving or cost-effective. This was done by using threshold values for incremental cost per life-year saved of $25,000, $50,000, or $75,000 compared with conventional tests at given screening intervals.

Results

Figure 1 shows the cost-effectiveness of screening at 1-, 2-, 3-, and 5-year intervals as sensitivity varied from 51% to 99% and specificity was held constant at 97%. With screening every 5 years, the variation in discounted life expectancy (measured on the vertical axis) is wide, whereas the range of costs (the horizontal axis) is narrow. As screening frequency increases, the effect of variability in sensitivity on effectiveness decreases and the effect on costs increases. The incremental cost-effectiveness ratio (the inverse of the slope of the line between two points on the graph) also increases with increasing sensitivity. Costs increase as sensitivity increases even at 5-year screening intervals. That effect is more pronounced as screening intervals decrease. For example, increasing sensitivity from 51–99% at no additional cost per test has an incremental cost per life-year of $7206 at 3-year screening intervals but $194,083 at 1-year screening intervals (Table 3).

Figure 2 shows the effect of varying specificity over a range of 80–99% while sensitivity was held constant at 51%. Costs increase as specificity decreases; the effect of

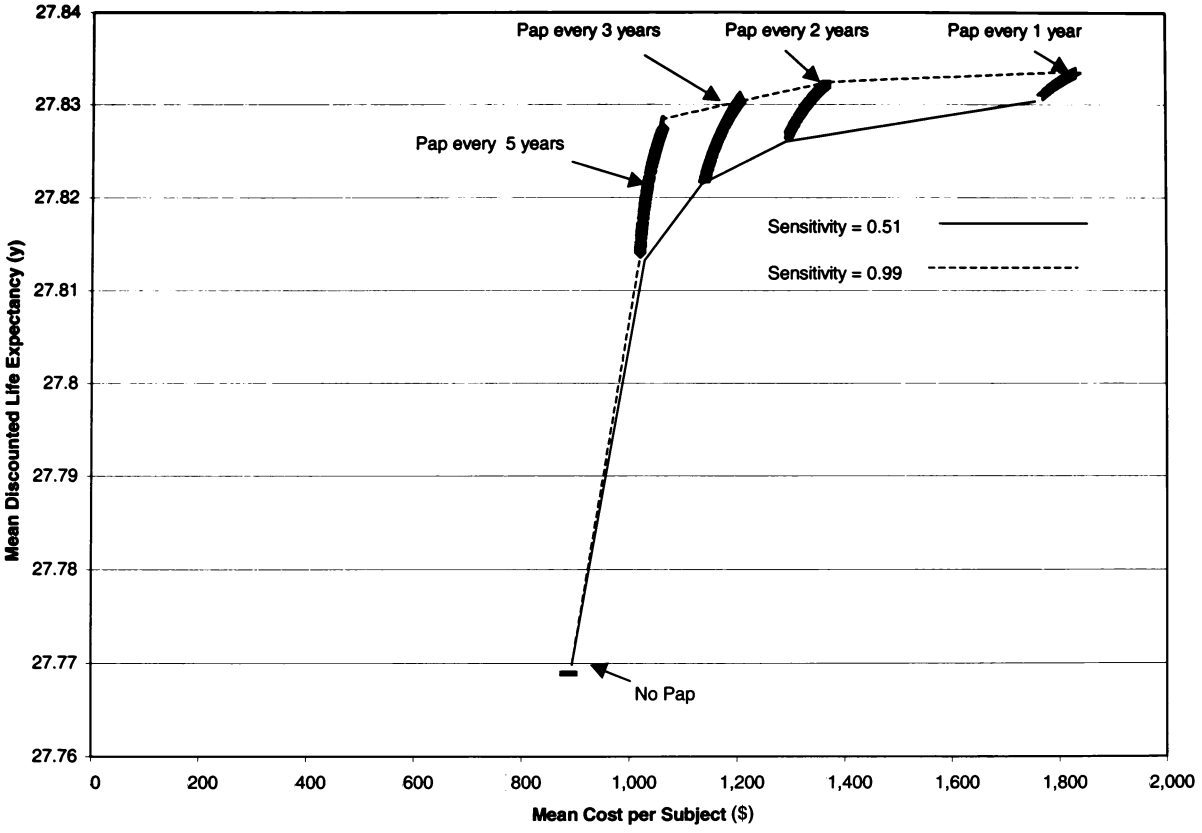

Figure 1. Effect of varying sensitivity from 51% to 99% at a constant specificity of 97% at various screening intervals on costs and life expectancy after 15 years of age. Costs and years of life are discounted at 3% annually, resulting in an apparently lower than expected life expectancy. Pap = Papanicolaou smear.

changing specificity is wholly on costs (the model assumes that colposcopy and biopsy resulting from a false-positive test has no effect on life expectancy). As screening frequency increases, the effect of variability in test characteristics also increases.

Multiway threshold analysis illustrates the joint effect of varying sensitivity, specificity, and frequency of testing on cost-effectiveness (Figure 3). All possible combinations of relative sensitivity (from 1.0–1.9) and specificity (from 0.75–1.0) are considered, for a screening interval of 3 years (*left*), 2 years (*middle*), and 1 year (*right*). The lines correspond to combinations of relative sensitivity and relative specificity that lead to an incremental cost-effectiveness ratio of $75,000, $50,000, and $25,000 per life-year saved (threshold values). Combinations in the upper right territory are more cost-effective; those to the lower left are less cost-effective.

Table 3. Effect of Varying Sensitivity on Incremental Cost Per Life-Year Saved

Strategy	Sensitivity*			
	51%	75%	87%	99%
No screening	–	–	–	–
Screening every 5 years ($)	2853†	2743	2812	2919
Screening every 3 years ($)	14,483	24,195	31,598	41,881
Screening every 2 years ($)	35,174	62,300	83,304	112,701
Screening every 1 year ($)	107,631	205,007	279,723	381,928

* Cytologic diagnosis of atypical squamous cells of undetermined significance or worse and histologic diagnosis of low-grade squamous intraepithelial lesion or worse.

† Each figure represents the cost per year of life saved compared with the row immediately above.

In univariate analysis, we found that the cost of diagnosis and treatment of low-grade SIL was the parameter that had the greatest effect on cost-effectiveness estimates. If a new technology has no extra cost per slide compared with conventional tests, increasing sensitivity was cost-saving with 3-year screening intervals if the cost of evaluating and treating low-grade SIL was $550, a value below the 25th percentile for our cost data. That was the only variable and only screening frequency that resulted in cost-savings. At any marginal per slide cost above $3, increasing sensitivity was not cost-saving even if the cost of treating low-grade SIL was $0.

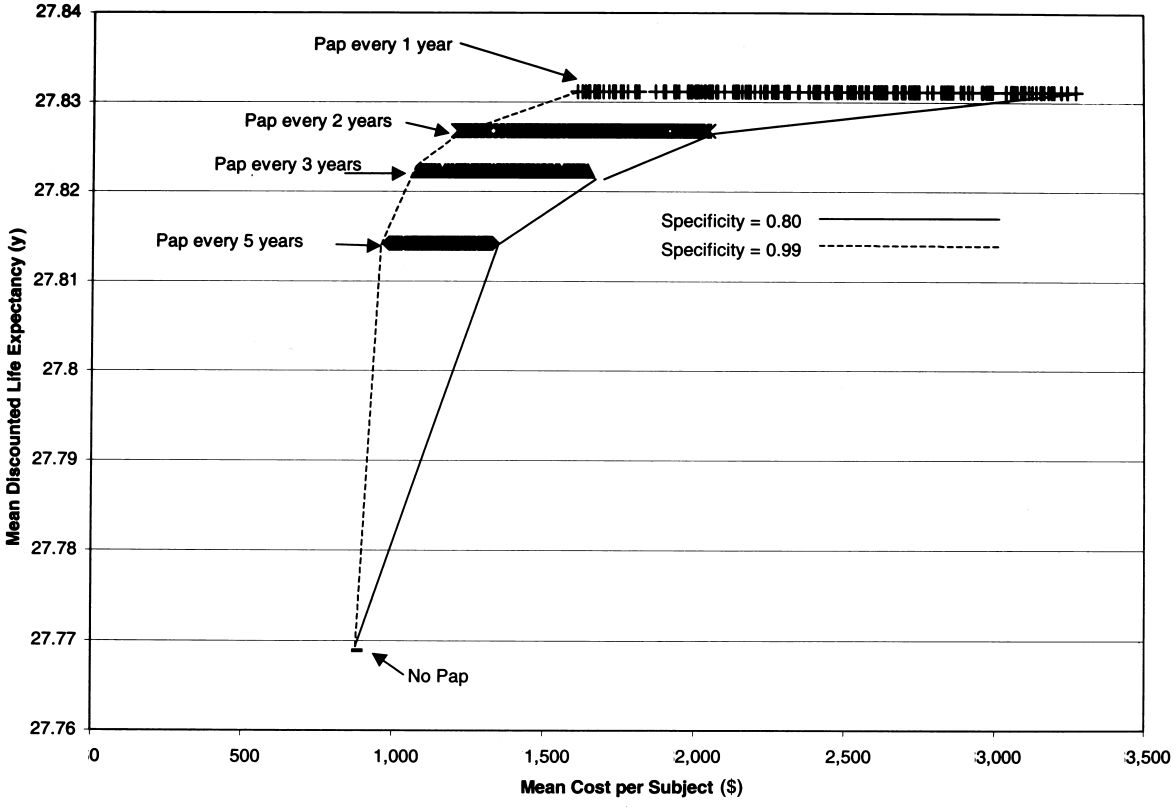

Figure 2. Effect of varying specificity from 80% to 99% at a constant sensitivity of 51% on costs and life expectancy after 15 years of age. Costs and years of life are discounted at 3% annually, resulting in an apparently lower than expected life expectancy. Pap = Papanicolaou smear.

Discussion

We found that in our base case, increasing sensitivity always led to increased screening costs, even at relatively infrequent screening intervals. For a given screening interval, a new technology that increases sensitivity, even at a very low marginal cost per slide compared with conventional Papanicolaou smears, will disproportionately increase cost relative to health benefit as measured in years of life saved.

New tests with improved sensitivity led to substantially greater cost than health benefit, which relates to

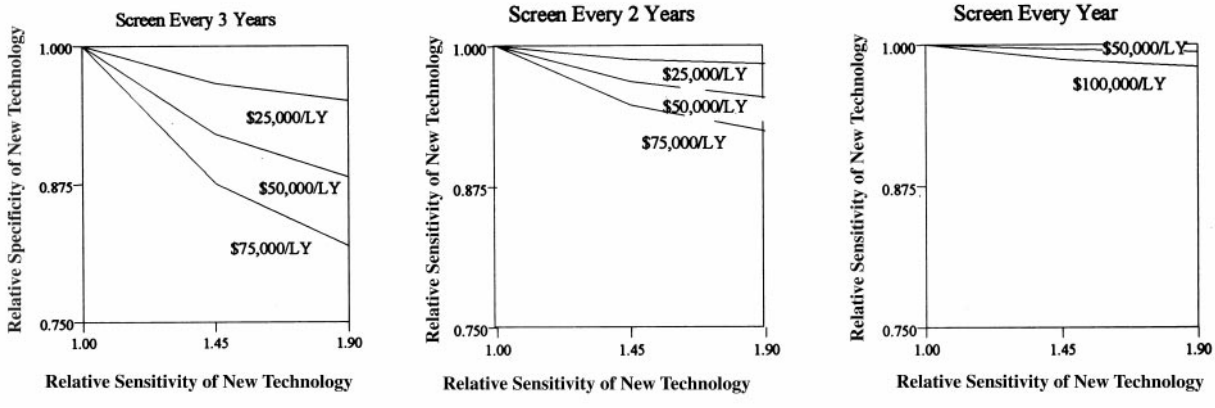

Figure 3. Two-way sensitivity analysis on effects of relative sensitivity and specificity of a hypothetical new technology (at a marginal cost of $0) relative to conventional Papanicolaou smear on cost-effectiveness at 1-, 2-, 3-, and 5-year screening intervals. Lines indicate thresholds at which the incremental cost-effectiveness of the new technology relative to that of a conventional Papanicolaou smear equals the indicated amount. Areas of the graph above each line indicate combinations of relative sensitivity and specificity at which the incremental cost-effectiveness ratio is less than the threshold value. LY = life-years saved.

the natural history of HPV infection and cervical carcinogenesis. Although HPV infection is very common, the proportion of lesions that progress to high-grade SIL and cancer is small. At the population level, most extra lesions detected by reducing the rate of false-negative screening results will be unlikely to ever progress to invasive cancer. Although some improvement in life expectancy is gained, it is relatively small, especially at frequent screening intervals.

We also found that small changes in test specificity can have a great effect on cost-effectiveness estimates. This finding is important because increased sensitivity is unlikely to be achieved without some decrease in specificity. Thus, to improve cytologic screening, documentation of specificity of new technologies relative to conventional tests is essential.

Our analysis had several limitations, as does any model, and there was a high degree of uncertainty surrounding many of our parameters. However, we did extensive sensitivity analyses, varying model parameter estimates over a wide range of values, and found no change in our conclusions about incremental cost-effectiveness. The model used cross-sectional epidemiologic data to validate assumptions about incidence, prevalence, and lifetime risk, and because cross-sectional data reflect the experience of multiple successive cohorts, some parameters may have been overestimated or underestimated for certain age groups or populations. There might be some very high-risk populations (eg, HIV-infected women) for whom more sensitive screening at more frequent intervals would be cost-effective.[31] However, given the size of the incremental cost-effectiveness ratios and the robustness of the findings over a wide range of parameter estimates, it seems unlikely that results would differ for most women at average risk in the United States. We did not include direct nonmedical costs, such as lost wages, child care, or travel expenses. With the relative prevalence of low-grade lesions, including such costs would probably cause even higher cost-effectiveness ratios. We did not adjust life expectancy for quality of life. Without some measure of morbidity associated with treatment of invasive cervical cancer, models that focus only on life expectancy might underestimate benefits of improved screening strategies. Early-stage cervical cancer has a high survival rate; therefore, failure to detect premalignant lesions that are later detected as stage I invasive cancers will not decrease life expectancy dramatically. Treatment options for all but the most minimally invasive cervical cancers are limited to radical hysterectomy and radiation, both of which have substantial risks for short-term and long-term morbidity.[32] An alternative approach to estimating morbidity is to apply data on various treatments for different stages of cervical cancer to the predictions of the model to generate estimates of numbers and types of treatments of cervical cancer from various screening strategies.[7] Quality-of-life issues beyond treatment for cervical cancer also must be considered. Given the high incidence of HPV infection and low-grade lesions compared with cervical cancer, most women are much more likely to receive diagnosis of and treatment for low-grade lesions than cervical cancer. Because any degree of abnormality on Papanicolaou smears can have substantial emotional effects,[33] a true estimate of effects of cervical cytologic screening strategies on overall quality of life must include all aspects of screening, not just treatment of cervical cancer. Most of our parameter estimates were derived from United States data and may not be generalizable to other settings.

The main implication of our analysis for policy was that a large proportion of costs associated with new technologies are the consequence of improved sensitivity. New, more sensitive technologies are likely to be cost-effective compared with conventional tests only if they are associated with improved specificity, permit decreased screening frequency, or are used in conjunction with less expensive treatments of low-grade abnormalities. Increased test sensitivity alone is not sufficient to improve tests. New tests based on specific HPV types[34,35] or that use biomarkers[36] might meet all three requirements.

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Address reprint requests to:
Evan R. Myers, MD, MPH
Duke University Medical Center
Department of Obstetrics and Gynecology
DUMC 3279
Durham, NC 27710
E-mail: myers008@mc.duke.edu

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