INTRODUCTION

Given that screening can be an effective method of reducing morbidity and mortality from cervical cancer in elderly women, what are the actual likely costs and outcomes that would result from screening women in this group? This chapter describes a cost-effectiveness analysis that assesses the health and cost impacts of different Pap smear screening alternatives for elderly women who are screened. The chapter then examines some of the implications of the model results for the Medicare program.

THE COST-EFFECTIVENESS MODEL

Description

The model examines the relative costs and effectiveness of four different screening alternatives:

- one-time screening at age 65,
- screening every 5 years (beginning at age 65),
- screening every 3 years, and
- annual screening.

A Markov model (described in app. E) is used to simulate the process of screening, diagnosis, and treatment in a hypothetical population of one million women, beginning at age 65. Because one purpose of the model was to lend insight into the usefulness of a Medicare benefit, and because Medicare has no records on most individuals before they reach age 65, the model assumes that nothing is known about the specific screening history of any individuals before that age.

Five states of health are included in the model and are labeled as follows:

- healthy,
- CIN (corresponding to cervical intrae - pithelia neoplasia (CIN) grades 1 and 2--mild and moderate dysplasia),
- CIS (corresponding to CIN grade 3--severe dysplasia and carcinoma *in situ* (CIS)),
- early invasive cervical cancer (EICC, corresponding to stage I cancer), and
- late invasive cervical cancer (LICC, corresponding to stages II, III, and IV).

Within each state of health, two possible substates exist; a woman's condition may be *unrecognized (i.e.,* not yet brought to the attention of the medical system) or *recognized (i.e.,* diagnosed through screening or through the diagnostic evaluation of symptoms). (Following the logic that "recognized" indicates further contact with the medical system, "healthy-recognized" is the label given in the model to healthy women who have false-positive Pap smear results and thus undergo diagnostic workups.) An additional state is included to represent deaths as the model progresses.

The simulation program tracks the progress of the hypothetical cohort of 1 million 65-year-old women until they reach age 109. The remaining survivors are assumed to die before reaching age 110. Each iteration of the model corresponds to 1 year. Running tallies are maintained of the number of smears performed, the number of cases diagnosed at each disease stage, and overall cohort survival.

A significant limitation of the Markov model as it is applied here is that all tumors are assumed to have a constant probability of moving from one state to another in any given time period. In real life there are likely to be multiple populations of tumors with different progression rates depending on etiology, host factors, and so forth. Cruciaaly, a screening program will be most sensitive to finding the slowly progressing lesions (length bias), leading to an overestimate of the program's effectiveness in preventing

mortality. The importance of this issue in interpreting the model results is discussed at the end of this chapter.

Assumptions

Model Inputs

A Markov model simulation requires two sets of inputs (app. E). First, one must specify the proportion of subjects in a cohort falling into each state at the outset--i. e., the proportion of 65-year-old women who are healthy, have CIN, etc. In this model, the proportion of women who begin the model in a state other than healthy corresponds to the prevalence of CIN, CIS, EICC, and LICC in women at age 65. The probability of starting in the healthy state is simply one minus the total of the other probabilities. All women begin the model in an unrecognized substate.

Second, one must specify, for each state, the probability that a woman will move to a different state (e.g., from CIN to CIS) during each iteration of the model (i.e., per year). Not all movements between states can occur; no cases can move out of the dead state, for example. Only the following types of transitions are allowed in this model:

- *recognition* --transition from an unrecognized state to the corresponding recognized state (through screening or diagnosis);
- clearance--transition from one healthy substate to the other by ascertaining that a Pap smear result was a false positive (somewhat counterintuitively, this corresponds to transition from "healthy-recognized" to "healthy-unrecognized");
- *progression* --transition to the next most advanced disease state (e.g., CIN to CIS);
- *regression or cure--permitted* only for transition from CIN or CIS to the healthy state; and
- death--transition to the dead state from any other state.

In any year, women who do not make one of these transitions remain in their current state.

The specific numbers used as inputs to the model are derived from the medical studies described in chapter 2. For most relevant aspects of cervical cancer in elderly women, no definitive studies or unified consensus exists. Thus, to enhance confidence in the results of this model, a range of estimates for each data element was obtained. A base case was chosen to represent the "best estimate" of the true value of the data item. A high estimate and a low estimate are chosen as well, in order to test the sensitivity of the base-case results to the model assumptions. Such sensitivity analyses can enhance confidence in the overall conclusions of the simulation and identify the areas where uncertainty has the greatest implications. The various estimates are presented in table 11 and discussed briefly below. Appendix F presents the rationale for selecting specific estimates in greater detail.

Recognition Probabilities--For women with disease, the probability of transition from an unrecognized to a recognized state in the model is dependent on the sensitivity of the Pap test.[1] For healthy women, "recognition" depends on the specificity of the test--i.e., the rate at which healthy women are falsely identified as having disease. Base-case rates of sensitivity and specificity used in the model are within the range of estimates reported in the literature, but they are from the low end of that range to accommodate the likelihood that real-world accuracy for Pap smears from elderly women is somewhat lower than the test accuracy found in carefully monitored studies and studies of younger women.

Women with CIN and CIS can have their disease recognized only through screening. Invasive cancer, however, may also become recognized as a result of symptoms. Reliable

1 The actual probability for women with CIN and CIS is the product of test sensitivity and survival probability; for women with EICC and LICC, the rate of development of symptoms is an added factor.

Table n--Cost-Effectiveness Model Input Data Assumptions

		Data assumptions		
		Lou	Base	High
Pap smear sensitivity and specificity				
Sensitivity for:	CIN	.50	.75	.00
	CIS/EICC/LICC	.50	.75	.82
Specificity		.87	.95	.99
Annual probability of recognizing disease due to symptoms				
EICC		.07	.12	.27
LICC		.80	.80	.80
Initial state distribution for Pap smear simulation				
HEALTHY		.99013	.98721	.97940
CIN		.00380	.00480	.00580
CIS		.00239	.00239	.00620
EICC		.00081	.00280	.00559
LICC		.00287	.00280	.00301
Age-group-specific mortality rates for invasive cervical cancer				
EICC mortality at age:	65-69	.076618	.076618	.076618
	70-74	.070786	.070786	.070786
	75-79	.078677	.078677	.078677
	80-108	.138621	.138621	.138621
	109	1.0	1.0	1.0
LICC mortality at age:	65-69	.151742	.151742	.151742
	70-74	.172282	.172282	.172282
	75-79	.217248	.217248	.217248
	80-84	.281017	.281017	.281017
	85-108	.331627	.331627	.331627
	109	1.0	1.0	1.0
Annual probabilities of progression between states (per 1,000 cases)				
HEALTHY --> CIN		.94	3.28	5.41
CIN --> CIS		73.6	178.0	267.0
CIS --> EICC		181.0	261.0	632.0
EICC --> LICC		220.0	390.0	860.0
Annual regression rate (per 1,000 cases)				
CIN		5.4	38.1	265.0
CIS		0.0	0.0	201.0
Annual cure rate (Per 100 cases)				
CIN		85.0	95.0	98.0
CIS		90.0	98.0	98.0

Key: CIN--cervical intraepithelial neoplasia (grades 1 and 2)
CIS--carcinoma in situ and severe dysplasia
EICC--early invasive cervical cancer
LICC--late invasive cervical cancer

SOURCE: Office of Technology Assessment, 1990. See appendix F for sources of information and basis for individual data assumptions.

data on the rates of symptom development are not available. The assumptions regarding the likelihood of symptom development are based on data on the stage distribution of cancers at diagnosis, the probability of progressing from EICC to LICC, and the assumption that the great majority of women with LICC will develop symptoms within a year (app. F).

Clearance- -Clearance occurs when a woman with a false-positive test undergoes a comprehensive diagnostic workup. It is assumed that all false positives are identified in this workup.[2]

Progression, Regression/Cure, and Death Probabilities--Some research suggests that the probability of progressing from one state of neoplasia to the next is dependent on age (32). Base-case estimates in the model are thus derived from age-dependent data reported in the literature. The age-dependent assumption may not be correct; however, the high and low estimates of progression probabilities encompass a range of probabilities that includes data from other age groups.

Women with CIN or CIS may exhibit spontaneous regression to the healthy state. Women with recognized disease may revert to the healthy state subsequent to treatment (cure). Women with CIS are actually considered to be slightly more likely to be cured by a single treatment than women with CIN, because more women with CIS undergo very aggressive treatment (e.g., total hysterectomy). Consequently, there is a slight increase in the number of cases in which the lesion is entirely removed with a single treatment.

Death rates in the model for women in healthy, CIN, or CIS states are based on national, age-specific, all-cause mortality data (164). They are considered highly reliable assumptions and do not appear in table 11.

The situation for invasive cancer--EICC and LICC--is different. Although some women with EICC are probably cured, data to estimate the probability of this are not available. This model therefore does not permit transitions from the invasive cancer states back to earlier states. Consequently, the model probably slightly overestimates morbidity from invasive cancer; once a woman moves into the EICC state, she will be categorized as having invasive cancer until she dies. This does not affect her chance of survival in the model, however. The death probabilities in the model for women with invasive cancer are based on all-cause mortality data specific to the cohorts of women diagnosed in each stage of cervical cancer. Thus, for a woman with EICC, the statistical likelihood of dying in the model depends only on the fact that she was once diagnosed with EICC, not on the fact that the model continues to classify her in that category.

Service and Cost Assumptions

Each woman in the model diagnosed with CIN, CIS, EICC, and LICC incurs the costs of diagnosis, treatment, and followup associated with that state. At any given screening frequency, a single iteration of the model (representing the passage of a year of time) is accompanied by a specific number of women newly diagnosed in each state. These women then begin to accrue the costs associated with those diagnoses. At the end of the simulation, the total costs associated with each screening frequency can be tallied and compared.

The costs of screening itself and of clearing false-positive cases are also included in the total costs for each screening frequency. In the model, a "positive" test is any

2 A special feature of this model is that the healthy- recognized state is a "virtual" state: after entering that state and being tallied (so that costs of work-up can be assessed), these women are returned to the healthy-unrecognized state immediately, rather than waiting for the next year.

Pap smear result that leads to a further investigation of the possibility of neoplasia. A "false-positive" test is any so-defined positive smear in which the investigation does not lead to a diagnosis of neoplasia, even if some other condition is diagnosed and followed up. This model considers neither the additional costs nor the additional benefits incurred after this point from the incidental diagnosis of other conditions. The cost of a workup to clear a false positive is equivalent to the diagnostic segment of care for CIN.

To calculate the average cost per woman in each state (CIN, CIS, EICC, and LICC), a set of services related to the diagnosis, treatment, and followup of each state were specified. The specified protocol is based on current oncological practice, supplemented by observations of members of an expert panel from their clinical experience (app. C). Modifications were made in the indicated protocol based on statistical data from the National Hospital Discharge Survey, which made possible an analysis of the proportion of hospitalized elderly women with a given diagnosis who actually received specific services. It must be emphasized that the resultant modified protocol is not, and is not intended to be, an example of an ideal protocol for treating cervical neoplasia. Rather, it is an approximation of actual current practice.

Table 12 summarizes the total costs for all services described below.[3] The itemized components of these costs and the calculation of total cost for each service package (e.g., treatment of CIS) are detailed in appendix F.

Table 12--Summary of Cost Estimates for Different Components of Ca

Component	Diagnosis/ treatment	Followup	Total
CIN.	$ 669.65	$ 432.71	$1,102.36
CIS.	3,925.96	432.71	4,358.67
EICC.	8,033.70	1,182.76	9,215.76
LICC.	12,232.00	1,126.76	13,358.76
False positives:	$ 575.51	$ --	$ 575.51
Screening:	$ 11.37 (base estimate)		
	11.37 (low estimate)		
	43.25 (high estimate)		

[a]Cost per woman with indicated condition when it occurs. (Costs as presented in this table are undiscounted; they are discounted at the point in the model where they are incurred.)

KEY: CIN--cervical intraepithelial neoplasia
CIS--carcinoma in situ
EICC--early invasive cervical cancer
LICC--late invasive cervical cancer

SOURCE: Office of Technology Assessment, 1990. See appendix F for calculation of individual costs.

Screening --All women are screened in the model (except in the no-screening scenario). The updated Medicare average allowed charge for a simple Pap smear and associated specimen collection fee ($11.37) is used as the assumed cost of the screening service for both the base case and the low estimate.[4] The high-cost estimate for screening includes the cost of a limited visit to a gynecologist as well as the cost of the test itself. If the result of Pap smear screening is

3 The estimate of the total cost of late cancer care, $13,266, is lower than estimates by other analysts based on 1974-1981 data from the Continuous Medicare History File (5). Their analysis would lead to an estimated total cost of approximately $7,000 for a woman dying of cervical cancer 2 years after diagnosis. Their estimates are not directly usable in this cost-effectiveness analysis because they do not distinguish between cases diagnosed in early versus late stages, as is required for this model. In addition, changes in clinical practices, substitution of outpatient for inpatient locations, and so forth, make it desirable to avoid reliance on data from the 1970s.

4 The Medicare average allowed charge for a service is used as the basis for Medicare payments to health care providers; Medicare pays a proportion of the allowed charge for all covered services. Actual physician and laboratory charges may be higher than the Medicare allowed charge.

negative, the patient receives no further service, and she is returned to the population with the expectation of routine rescreening at the time interval under study (e. g., in 5 years).

Diagnosis--If the result of the screening is positive for abnormal cells, a COlPOSCOPY is done (assumed to require an office visit). Subsequent procedures depend on the adequacy and results of COlPOSCOPY, as follows:

- If a satisfactory view is obtained at colposcopy, then positive cases undergo a directed biopsy. Negative cases repeat the Pap test. If it, too, is negative, the case is returned to the population, but if it is positive, ionization is performed. This is an inhospital procedure.
- If colposcopy does not provide satisfactory visualization of the suspect area, ionization is done. If the finding is negative, the Pap test is repeated, and if that is positive, other biopsies are done; if the Pap test is negative, the patient is returned to the population. If the conization finding is positive, the case is diagnosed as CIN, CIS, or invasive cancer.

This is the extent of the diagnostic workup for women with false-positive tests and for women with CIN or CIS. Women with invasive cancer must also undergo a staging workup to determine the extent to which the cancer has spread. The staging protocol includes chest X-ray, pelvic computed tomography scan, sigmoidoscopy, barium enema, cystoscopy, intravenous urography, and blood tests (complete blood count, blood urea nitrogen, and creatinine determination).[5] Most of this protocol can be completed on an outpatient basis, although a minority of women (20 percent of those with EICC and 30 percent with LICC) receive the workup as hospital inpatients.

Treatment--For CIN, treatment options include cryosurgery, cauterization, and laser surgery, while for CIS the options are therapeutic ionization or hysterectomy. It is assumed that all true-positive CIN cases, and all CIS, EICC, and LICC cases, are treated. The assumed frequency with which various procedures are undertaken is drawn from existing hospital discharge data on patients with cervical cancer (app. D).

EICC treatment options are implantation of radioactive agents and/or hysterectomy. LICC options include distant radiation, chemotherapy, pelvic exenteration, or combinations of these. Some advanced cases are admitted to hospitals for supportive terminal care. (This protocol probably underestimates the actual total costs of LICC, since it does not include some relevant outpatient services--e. g., the cost of drugs to reduce pain.)

Followup Services and Costs--Each condition that requires treatment is assumed to have attendant 5-year followup costs. The services associated with followup of different disease states are adapted from Mandelblatt and Fahs (91).[6] The specific services and associated costs are presented in detail in appendix D for each disease state. In summary, the protocol for 5-year followup of each state is as follows:

- *CIN and* CIS--office visits and annual Pap smears for all patients. A small proportion of patients undergo repeat treatments (cryosurgery or ionization) during the first followup year.
- ElCC--office visits and various diagnostic tests, including intravenous

5 The use of ultrasound evaluation in place of some other tests is gaining favor in some institutions, but since the practice is apparently not yet widespread and there are no data on its frequency, it is not reflected in the cost assumptions of this model.

6 In pricing the followup services, clinic visits in their protocol are replaced by physician office visits for applicability to the general population of elderly women.

pyelograms (IVPS), chest X-rays, and pelvic sonograms. Numbers of visits and tests are greatest in the first year.
- LICC--office visits, IVPS, and chest X-rays in followup years 1 through 3; office visits, an IVP, a chest X-ray, and a pelvic sonogram in each of years 4 and 5.

Followup accounts for 8 percent of the total cost of LICC, for 12 percent of EICC, and for 9 percent of CIS costs. Since CIN evaluation is not very costly compared to evaluation of these other stages, followup amounts to 38 percent of total cost per CIN case.

Results

This model calculates the health care costs associated with screening, diagnosis, and treatment of cervical neoplasia at each alternative screening frequency. The benefits calculated include only the years of life saved by implementing screening. Other potential costs (e.g., cost of medical care for conditions unrelated to cervical cancer in those life-years saved) and other benefits (e.g., disability days avoided) are not considered. Both costs and life-years saved are discounted in the reported results.'

The results of the cost-effectiveness model under base-case assumptions are shown in tables 13 through 15. They are presented for 3, 5, and 7 percent discount rates. The discussion below focuses on the base-case results for a 5-percent discount rate.

Health Effects of Screening

In the base case, 14,400 discounted life years are gained for the model cohort of one million women by instituting a single screening at age 65 (table 13). There are successive increments in discounted life-years gained as the intensity (frequency) of screening is increased, although the size of the increase declines at frequencies greater than 5 years. In progressing from a 5-year to a 3-year schedule, for example, the incremental gain is reduced to 7,000 life-years. There is some gain at every increase in screening frequency, however, so total life-years of the cohort are greatest at the most frequent screening schedule. Annual screening adds 50,000 more years of life than no screening at all, or an average of 18 more days of life per woman in the cohort.

Table 13--Model Results: Life-Years Saved (Base-Case Assumptions)[a]

Discount rate and screening schedule	Years of life of cohort (in thousands)	
	Total	Additional
3% discount rate		
No screening	13,364.9	·
One-time at 65	13,384.2	19:3
Every 5 years	13,416.1	31.9
Every 3 years	13,425.8	12.7
Every year	13,435.2	9.4
5% discount rate		
No screening	11,383.1	·
One-time at 65	11,397.5	14.4
Every 5 years	11,419.3	21.8
Every 3 years	11,426.3	7.0
Every year	11,433.1	6.8
7% discount rate		
No screening	9,877.4	·
One-time at 65	9,888.4	11.0
Every 5 years	9,903.5	15.1
Every 3 years	9,908.6	5.1
Every year	9,913.7	5.1

'Per 1 million women beginning at age 65,

SOURCE: Office of Technology Assessment, 1990.

The added years are expected to be of good quality, because they are obtained through the prevention of late-stage cancer cases, not just through extending life for women with late-stage disease. (As table 14 shows, the number of cases of LICC decreases from 23,500 with no screening to

7 Discounting accommodates the economic assumption that something of value received today is worth more than that same thing received later. A 5 percent discount rate assumes that a $100 benefit (or cost) 1 year from now is equal to a $95 benefit (or cost) today. Discounting thus displays all benefits or costs in their present value.

Table 14--Model Results: Numbers of Smears Taken and Cases Detected (Base-Case Assumptions)[a,b]

	Number		Cases			
	Smears (millions)	False positives	CIN	CIS	EICC	LICC
No screening	--	--	--	--	34,461	23,532
One-time at 65	1.0	49,361	3,600	1,306	30,825	20,211
Every 5 years	4.1	199,570	29,257	8,180	14,281	8,162
Every 3 years	6.4	317,340	38,829	7,705	9,731	5,854
Every year	18.3	910,141	53,824	3,511	4,524	4,099

[a]The same actual numbers of cases accrue for each screening alternative regardless. Only the ultimate value of those expressed as life-years saved, is discounted.
[b]Per 1 million women beginning at age 65.

KEY: CIN--cervical intraepithelial neoplasia; EICC--early invasive cervical cancer
CIS--carcinoma in situ; LICC--late invasive cervical cancer

SOURCE: Office of Technology Assessment, 1990.

4,100 cases with annual screening.) Women live longer because they are cancer-free, or because they have early rather than late cancer. The cost of increasing years of cancer-free life among some members of the group, however, is increased detection and treatment of CIN. Some women whose CIN is detected and treated would not have gone on to develop invasive cervical cancer in their lifetimes. For these women, screening does not improve the quality of life; rather, it brings with it only the psychological costs and physical discomfort of undergoing the diagnostic and treatment procedures. This problem is greatest with annual screening, where the greatest number of CIN cases are detected.

costs

The costs associated with cervical cancer, including screening, diagnosis, treatment, and identification of false positives, are shown in detail in table 15. Total costs of services are higher with screening than without it, and they increase as the frequency of screening increases. The total cost of cervical cancer care for the cohort (of 1 million women) in the absence of screening is $218 million in the base case. By comparison, the cost associated with the least-intensive screening schedule--one-time screening at age 65--is $242 million, an incremental cost of $24 million. Total costs increase as the screening schedule intensifies and rise dramatically for annual screening, which has a total cost of $585 million (an incremental increase of $270 million over an every-3-year screening schedule).

The relative cost-effectiveness of screening at various intervals depends on whether the increase in life-years gained as screening frequency increases is more rapid than the rise in total costs associated with more frequent screening. Comparison of costs and effects of different schedules produces a cost-effectiveness ratio showing the added cost per year of life gained by screening (table 16). In the base case this amount is $1,666 for a one-time screen, but it increases with frequency of Pap testing, so that moving from a 5-year to a 3-year schedule costs $5,956 per additional discounted life-year gained. Annual screening costs considerably more--$39,693 per discounted life-year added to the cohort's life expectancy.

Sensitivity Analyses

Favorable/Unfavorable Cases--This analysis tests the sensitivity of the model results to changing the base-case assumptions

Table 15--Model Results: Costs (Base-Case Assumptions)[a]

Discount rate and screening schedule	cost (in millions) Screening	Confirmation of false positives	Cost of care (in millions) CIN	CIS	EICC	LICC	Total costs (in millions)
3% discount rate							
No screening	$--	$--	$--	$--	$49	$212	$ 261
One-time at 65	11	28	4	6	54	177	281
Every 5 years	36	89	23	27	52	84	311
Every 3 years	56	139	31	26	42	64	358
Every year	156	392	44	13	24	48	677
5% discount rate							
No screening	$--	$--	$--	$--	$40	$178	$218
One-time at 65	11	28	4		46	147	242
Every 5 years	31	78	20	23	45	77	273
Every 3 years		120		22	38		315
Every year	132	333	37	12	23	48	585
7% discount rate							
No screening	$--	$-	$--	$ --	$33	$153	$ 186
One-time at 65	11	28	4	6	40	125	214
Every 5 years	28	69	17	20	40	72	245
Every 3 years	42	105	23	20	34	59	282
Every year	114	288	32	11	23	47	516

[a]Per 1 million women beginning at age 65.

KEY: CIN--cervical intraepithelial neoplasia, EICC--early invasive cervical cancer
CIS--carcinoma in situ, LICC--late invasive cervical cancer

SOURCE: Office of Technology Assessment, 1990.

Table 16--Cost-Effectiveness of Screening Under Alternative Screening Assumptions: Base Case (5% Discount Rate)

Screening schedule	Discounted life-years' (in thousands) Cohort	Added	Costs (in millions) Total	Added	Cost-effectiveness ratio (added cost per life-year gained)
No screening	11,383.1		$217.79		
One-time at 65	11,397.5	14.4	241.78	$23.99	$ 1,666
Every 5 years	11,419.3	21.8	273.46	31.68	1,453
Every 3 years	11,426.3	7.0	315.15	41.69	5,956
Every year	11,433.1	6.8	585.06	269.91	39,693

[a]Per 1 million women beginning at age 65.

SOURCE: Office of Technology Assessment, 1990.

to more extreme high and low estimates (under a 5-percent discount rate). It includes:

- a "favorable" case in which all high and low input estimates most favorable to screening (e.g., high test accuracy, high prevalence) are combined; and
- an "unfavorable" case that combines all assumptions most unfavorable to screening.[8]

The specific set of high and low assumptions used for each case are presented in table 17; results are presented in table 18. Varying all assumptions in a direction favorable to screening results in absolute savings for all increases in Pap test frequency except for shifting from 3 years to 1 year. In addition, the gain in life years is substantially greater than in the base case. Compared to no screening, even a single screening gains 29,600 years of life. In contrast, if unfavorable assumptions are used, the greatest incremental gain occurs in going from no screening to a single screen but results in the addition of only 2,500 years of life. More frequent screening results in some additional gains, but at very high cost; at annual screening, the incremental cost per life-year gained is nearly $800,000.

High Risk/Low Risk Populations--In a further analysis, the model was applied separately to hypothetical cohorts of high-risk and low-risk women.

- The "high-risk" case includes assumptions of high incidence, prevalence, and progression rates and low regression rates (table 17). The low rate for symptom development for early cancer was also used, representing lower ability or willingness to enter the medical system after the development of mild symptoms of cancer. All other probabilities are as in the base case.
- The "low-risk" case assumes low incidence, prevalence, and progression rates; and high regression and symptomaticity rates. Other assumptions are as in the base case.

Marked differences in outcome were found for the two groups (table 18). For high-risk women, the gain in discounted life years was substantial throughout, and 5- and 3-year schedules result in actual cost savings. Even annual testing would cost less than $6,500 per incremental life-year saved. For low-risk women, gains were small for all but one-time testing. One-time testing yielded a cost-effectiveness ratio of $11,666 per life-year gained; cost-effectiveness ratios for more frequent intervals range from over $73,000 to nearly $500,000.

The "high-risk" and "low-risk" groups in the model do not directly correspond with known risk factors for individuals (e.g., past history of multiple sexual partners, no prior screening). The set of assumptions used to define these groups in the model, however, are those that most likely underlie higher real-world risk. A lack of prior screening, for example, means that any existing disease has not been detected; thus, elderly women with this risk factor would have higher average prevalence rates of neoplasia (one of the inputs for the high-risk group in the model).

Individual Sensitivity Analyses--In order to test the robustness of the clinical and economic assumptions used in the baseline model, one-way sensitivity analyses were performed for the worst-case assumption (either high or low estimate, depending on the parameter) for individual model parameters. For the previously described sensitivity analyses, the results compared the relative cost-effectiveness of screening under different screening schedules. To judge the effect of varying each individual parameter, however, all variables except the individual parameter of interest -- including the screening schedule -- are held constant. Thus, a single screening schedule must be chosen for the

8 High estimates of progression rates may be either favorable or unfavorable to screening, depending on how rapidly progression is assumed to occur in the base case. In this model, it turns out that lower estimates of progression rates are unfavorable, while higher estimates are favorable (table 17).

Table 17--Cost-Effectiveness Model Input Data Assumptions: Selected Sensitivity Analyses

	Data assumptions			
	Favorable/unfavorable[a]		High risk/low risk[b]	
Pap smear sensitivity and specificity				
Sensitivity for: CIN	.80	.50	.75	.75
CIS/EICC/LICC	.82	.50	.75	.75
Specificity	.99	.87	.95	.95
Annual probability of recognizing disease due to symptoms				
EICC	.07	.27	.07	.27
LICC	.80	.80	.80	.80
Initial state distribution for Pap smear simulation				
HEALTHY	.97940	.99013	.99013	.97940
CIN	.00580	.00380	.00380	.00580
CIS	.00620	.00239	.00239	.00620
EICC	.00559	.00081	.00081	.00559
LICC	.00301	.00287	.00287	.00301
Mortality rates for invasive cervical cancer				
(Same as base case for all alternatives--see table 9)				
Annual rate of progression between states (per 1,000 cases)				
HEALTHY --> CIN	5.41	0.94	5.41	0.94
CIN --> CIS	267.0	73.6	267.	73.6
CIS --> EICC	632.0	181.0	632.	181.0
EICC --> LICC	860.0	220.0	860.	220.0
Annual regression rate (Per 1,000 cases)				
CIN	5.4	265.0	5.4	265.0
CIS	0.0	201.0	0.0	201.0
Annual cure rate (Der 100 cases)				
CIN	98.0	85.0	95.0	95.0
CIS	98.0	90.0	98.0	98.0

[a]The 'favorable" sensitivity analysis combines all high and low assumptions most favorable to screening.
[b]The "unfavorable~ sensitivity analysis combines all assumptions least favorable to screening. The 'high risk~case assumes high incidence, prevalence, and progression rates and low regression rates, while the "low risk" case uses opposite assumptions for these factors. Other assumptions (e.g., test accuracy) are as in the base case.

Key: CIN--cervical intraepithelial neoplasia
CIS--carcinoma in situ
EICC--early invasive cervical cancer
LICC--late invasive cervical cancer

SOURCE: Office of Technology Assessment, 1990. See appendix F for sources of information and basis for individual data assumptions.

Table 18--Cost-Effectiveness of Screening Under Alternative Screening Assumptions: Selected Sensitivity Analyses (5% Discount Rate)[a]

Screening schedule	Discounted life-years[a] (in thousands) Cohort	Added	costs (in millions) Total	Added	Cost-effectiveness ratio (added cost per life-year gained)
Favorable case					
No screening	11,264.3		$ 553.75	$ --.-"	$ ...
One-time at 65..	11,293.9	29.6	531.18	-22.57	*
Every 5 years	11,343.3	49.4	436.33	-94.85	*
Every 3 years	11,366.9	23.6	400.54	-35.79	*
Every 1 year.	11,395.0	28.1	430.27	29.73	1,058
Unfavorable case					
No screening	11,439.5	·	$ 52.87	$ -----	$ ...
One-time at 65..	11,442.0	2.5	173.09	120.22	48,088
Every 5 years	11,442.8	0.8	382.37	209.28	261,600
Every 3 years	11,443.3	0.5	557.19	174.82	349,640
Every 1 year.	11,444.4	1.1	1,434.46	877.27	797,518
High-risk women					
No screening	11,264.3	·	$ 553.75	$ -----	$ ---
One-time at 65..	11,292.3	28.0	554.95	1.20	42
Every 5 years	11,338.9	46.6	504.34	-50.61	*
Every 3 years	11,362.1	23.2	502.80	-1.54	*
Every 1 year.	11,392.3	30.2	697.41	194.61	6,444
low-risk women					
No screening	11,439.5	·	$ 52.87	$ -----	$ ...
One-time at 65..	11,443.3	3.8	97.20	44.33	11,666
Every 5 years	11,444.3	1.0	170.54	73.34	73,340
Every 3 years	11,444.8	0.5	230.80	60.26	120,520
Every 1 year.	11,445.4	0.6	530.42	299.62	499,367

*Cost-saving.

[a]Per 1 million women beginning at age 65.

SOURCE: Office of Technology Assessment, 1990.

analysis. Results for the one-way sensitivity analyses below are based on comparing a 3-year screening schedule with no screening. They can be contrasted with the analogous comparison under the base case, where 3-year screening (compared to no screening) costs $2,254 per life-year gained. (Note that this figure is substantially different from the figure presented earlier, which was the incremental cost-effectiveness of 3-year compared to 5-year screening.)

- Test Accuracy--Low estimates for expected rates of sensitivity and specificity affect the efficiency of the program considerably. With the low assumptions, comparing a 3-year screening schedule to no screening, 34,200 life years are gained for the cohort at an added cost of over $303 million, or $8,866 per life-year gained. In other words, if test accuracy deteriorated from base-case to low-case estimate--all else equal--the deterioration in test accuracy would cost nearly $7,000 more per life-year saved than what could otherwise have been achieved.
- Disease Prevalence--Lower prevalence rates have minimal effect. This happens because the model depends for the most part on prevalence rates only at initiation of the screening program.
- Disease Incidence and Progression--The model is much more sensitive to as-

sumptions regarding annual progression probabilities (including the probability of progressing from no disease to disease, that is, the incidence rate). The "worst-case" assumptions of progression probabilities result in a cost-effectiveness ratio of $11,971 per year of life saved in going from no screening to a 3-year cycle. It is the sensitivity of the model results to disease incidence and progression that is responsible for a large part of the much lower cost per life-year saved of screening high-risk women.

- Disease Regression and Cure--Estimates of low cure rates have a minimal effect on the results. However, the high estimates of annual regression probabilities raise the cost-effectiveness ratio substantially, with a rise to $8,851 for 3-year screening.
- Rate of Symptom Development--Assuming a lower rate of symptom development in early and late invasive cancer has minimal effect on cost-effectiveness ratios.

Conclusions

The cost-effectiveness model employed here examined the question: Given that a woman, beginning at age 65, gets screened for cervical cancer, what is the relative cost effectiveness of different screening schedules? The model found that, under base-case assumptions (5-percent discount rate), the lowest cost per life-year saved for screening elderly women is obtained with an every 5-year screening frequency, which costs $1,453 per life-year saved. The incremental cost per year of life saved is progressively greater as screening frequency increases, amounting to $5,956 per life year for a 3-year screening cycle (compared to a 5-year cycle) and rising to $39,693 for annual screening. These cost-effectiveness ratios are comparable to other preventive health services for the elderly that have been legislatively mandated, such as the vaccine used to prevent pneumococcal pneumonia and mammography to prevent breast cancer (136,155,156).

It is likely that these findings underestimate somewhat the true cost per life-year saved of screening elderly women. The model assumes a constant probability of moving from one state to another during any given time period, which probably leads to an overestimation of screening benefits. In reality, tumors progress at varying speeds. Since screening programs are more likely to detect slow-growing tumors than fast-growing ones, [9] and since slow-growing tumors are presumably less likely than fast-growing ones to be fatal, the real benefits of screening are probably not as great as those predicted by this model.

Comparing some of the implications of this model to the estimates of other researchers does indeed suggest that this model overestimates the effectiveness of screening, although not dramatically so. The lifetime incidence of cervical cancer that this model predicts under the base case is about 3.5 percent for elderly women receiving no screening and about 1.4 percent for elderly women being screened every 3 years. Some other researchers, using data from the National Cancer Institute's database, have estimated a lifetime incidence for elderly women of less than 1 percent under existing screening conditions (where only one-half of elderly women have been screened within 5 years) (128). An overestimate in this model of the total lifetime likelihood of developing cancer would lead to a corresponding overestimate of lives saved from screening.

Results from the model suggest that the cost per life-year saved for high-risk women who receive screening is quite low (about $1,000 for annual screening and cost-saving for less frequent schedules), while the cost-effectiveness ratio for low-risk women is substantially higher (even for one-time screening). These results have major implications for any generalized screening program. For any given age group, the lowest-risk women have generally had the highest utiliza-

9 **See discussion of** length **bias (ch. 2., box C).**

tion of Pap smear screening programs. If this experience holds true for elderly women as a group, the cost per life-year saved is likely to be highest if the implementation of the benefit does not change the mix of women receiving Pap smears (i. e., mostly low-risk women being screened). If the proportion of screened women who are high-risk increases, the cost per life-year saved will decline, making the program more cost-effective. Thus, investing in outreach to increase utilization by high-risk women could reduce the incremental cost per year of life saved. (Total costs could even decrease if all screened women are high-risk, since for this group screening actually saves costs at 3- and 5-year screening frequencies.)

The cost-effectiveness model presented here is very sensitive to the accuracy of the Pap smear and certain assumptions about the natural history of disease. Estimates of lower and upper bounds for the cost-effectiveness ratios, incorporating these and other factors, are provided by the "favorable" and "unfavorable" sensitivity analyses that incorporate the high- and low-probability estimates that as a group are most favorable and least favorable to screening. The results of these scenarios imply that, under very optimistic assumptions, screening could pay for itself; under pessimistic assumptions, screening yields a positive benefit, but only at relatively high cost.

Considerable uncertainty regarding the epidemiology of cervical cancer in elderly women still exists, even about things so basic as whether the known risk factors predict risk in elderly women to the same extent as in younger women. Additionally, less is known about the natural history of the disease in the elderly than in younger populations. If the development of human papilloma virus (HPV) typing technology proves to predict cancerous outcomes more accurately than the Pap test alone, it will be particularly important to study the prevalence and predictive value of HPV infection in elderly women.

IMPLICATIONS FOR MEDICARE

Coverage Considerations

As of July 1, 1990, Medicare will pay for Pap smear screening tests up to every 3 years. More frequent screening of high-risk women is permitted under the law at the discretion of the Secretary of the Department of Health and Human Services (DHHS).

Medicare has always paid a proportion of the costs of cervical cancer. With no screening, under the baseline assumptions of the model used here, the lifetime financial costs of diagnosis, treatment, and followup of cervical cancer are estimated to average $218 per 65-year-old woman (in present dollars).

With Medicare coverage of Pap smear screening, costs to the program will almost certainly increase. The amount of increase (and the realized benefit) depends on: 1) the frequency of screening covered by the program, and 2) the extent to which beneficiaries utilize the service.

The frequency of the benefit is fundamental to a coverage decision. The cost-effectiveness analysis presented here does not have a "most" cost-effective solution, since additional benefits continue to accrue at each more frequent screening level, but it is generally consistent with the recently enacted benefit. The rapid rise in cost per life-year saved when screening frequency is increased from every 3 years to annually (in the baseline case) makes annual screening slightly more difficult to justify than less frequent screening for the overall elderly population. For high-risk women, however, even annual screening yields substantial benefits at modest cost per life-year gained. (In contrast, for low-risk women, very frequent screening yields virtually no incremental benefits over less frequent screening.)

Two different approaches are theoretically available to consider the different needs and potential benefits for women at different levels of risk of developing cervical cancer. The first approach is to set a Medicare benefit for which all elderly women are eligible, leaving it to each woman and her physician to determine the most appropriate actual screening strategy for that woman. This approach could be supplemented with outreach programs targeted towards high-risk women, since these women are less likely to participate otherwise but reap the greatest benefit from screening. Outreach in this case could range from educational programs to direct financial incentives, such as free screening at public health clinics.

A second approach is to differentiate in a Medicare benefit itself between high- and low-risk women, through a proxy of risk. One potential proxy of risk is a record of previous screening; thus, for example, Medicare might pay for screening at some specified frequency, but only until a woman had a Medicare-documented history of screening (e.g., up to a maximum of 3 tests). A second potential proxy of risk is evidence of low income; thus, Medicare might differentiate between women who are and are not dually eligible for Medicare and Medicaid when providing benefits. Medicare might pay for both the visit and the screening test for women who are also Medicaid-eligible, for example, but pay only for the test itself for other women. These two proxies -- number of previous screens under Medicare and eligibility for other programs, such as Medicaid or Supplemental Security Income-- could be combined in various ways as well.

The existing new law combines elements of both approaches. A general benefit is set by law, but the law empowers DHHS to provide differential benefits to high- and low-risk women. Whether DHHS acts on this option may depend in part on the administrative difficulty of a differential benefit. Administrative concerns are not trivial; any new benefit for which eligibility depends on factors such as time since last screen, total number of past screens, and eligibility for other non-Medicare programs can rapidly become very complex and costly to administer. Minimizing the number of different factors on which the benefit depends would reduce this potential problem.

Quality and Reimbursement Considerations

The relative costs and effectiveness of Pap smear screening depend on the accuracy of the test as it is performed and evaluated in everyday practice.[10] Fewer false positives mean fewer unnecessary followup procedures; fewer false negatives mean fewer women diagnosed during the later stages of invasive cancer, when treatment costs are greatest and cure rates lowest. Improved accuracy may raise some costs, too, since more women with the disease (including those with CIN and CIS) will be diagnosed and treated.

Measures to improve Pap smear accuracy, and particularly those to improve the quality of cytologic evaluation, have their own costs. To make evaluation more accurate, for example, a laboratory might implement strategies such as:

- monitoring/testing programs to evaluate the proficiency of cytotechnologists,
- requiring cytotechnologists or pathologists to re-evaluate a proportion of negative slides,
- limiting the number of slides per day cytotechnologists can examine, and
- continuing education programs for cytotechnologists.

All of these strategies have been considered in the current debate of how to improve laboratory accuracy. In 1988, for example,

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10 A recent study of laboratory accuracy suggests that there is considerable room for improvement. Eight of eighteen laboratories surveyed by the American Society of Cytotechnology were found to have critical deficiencies in their cytology operations (171).

the Health Care Financing Administration proposed a set of requirements, including many of these features, that laboratories must meet in order to qualify for Medicare reimbursement (53 FR 29591). The proposal would also require that laboratory reports to physicians identify inadequate smears, employ detailed descriptions of abnormal smears, and include followup recommendations.

Whether voluntary or mandated, such strategies would likely raise provider costs, which in turn would probably raise the cost of screening to Medicare. This investment would likely improve the cost-effectiveness of screening, although it would raise overall program costs. (Note that it is not absolutely certain that implementation of these strategies would raise costs; e.g., a laboratory beset with costly lawsuits as a consequence of errors might conceivably see a net saving as a consequence of implementing quality-improving strategies.)

Some conflicts may arise between Medicare efforts to improve accuracy of Pap smears and the Medicare reimbursement structure. At present, reimbursement is structured to reward quantity rather than quality; laboratories (or physicians) are paid a set fee per smear, and laboratories reap the greatest profit by encouraging their cytotechnologists to process a maximum number of smears per day. Under this system, fear of medical liability lawsuits and physician dissatisfaction are the only counteracting pressures to improve quality. Strategies to improve evaluation accuracy might require raising Medicare reimbursement rates per smear if the current reimbursement structure were maintained.

Resource Considerations

Medicare coverage of routine Pap smear screening would almost certainly increase the utilization of the test and require more laboratory services to evaluate the additional smears. However, a perceived shortage of cytotechnologists already exists (163). Market responses to increased demand for cytotechnology services, such as raising salaries to draw people into the profession, would probably raise screening costs to Medicare. If Medicare reimbursement rates did not rise, an alternative result would likely be long lag times between sampling and evaluation, with consequent delays in diagnosis for women with positive tests.

Strategies to improve the quality of Pap smear evaluation have additional implications for the availability of services. Limiting the number of slides per day that cytotechnologists could evaluate would increase evaluation time per slide, presumably improving accuracy, but it would also increase the need for cytotechnologists. Again, increased screening costs to Medicare would probably result.

Automated cytologic evaluation of Pap smears might reduce the number of cytologists needed, easing the perceived shortage of these professionals. Such technology is under investigation (149), but its accuracy compared to manual cytologic evaluations is not yet established.