A Markov Decision Process Model for Cervical Cancer Screening Policies in Colombia

Raha Akhavan-Tabatabaei, PhD, Diana Marcela Sánchez, Thomas G. Yeung, PhD

Cervical cancer is the second most common cancer in women around the world, and the human papillomavirus (HPV) is universally known as the necessary agent for developing this disease. Through early detection of abnormal cells and HPV virus types, cervical cancer incidents can be reduced and disease progression prevented. We propose a finite-horizon Markov decision process model to determine the optimal screening policies for cervical cancer prevention. The optimal decision is given in terms of when and what type of screening test to be performed on a patient based on her current diagnosis, age, HPV contraction risk, and screening test results. The cost function considers the tradeoff between the cost of prevention and treatment procedures and the risk of taking no action while taking into account a cost assigned to loss of life quality in each state. We apply the model to data collected from a representative sample of 1141 affiliates at a health care provider located in Bogotá, Colombia. To track the disease incidence more effectively and avoid higher cancer rates and future costs, the optimal policies recommend more frequent colposcopies and Pap tests for women with riskier profiles. ***Key words:*** *cervical cancer; screening; Markov decision process.* ***(Med Decis Making XXXX;XX:xx–xx)***

Cervical cancer is the second most common cancer among women around the world and is the first cause of cancer-related deaths in Colombia.[1] This type of cancer affects the lower part of the uterus, also called the uterine cervix, which connects the body of the uterus to the vagina. Cervical cancer development starts with abnormal growth or behavior of cervical cells. Furthermore, for cervical cancer development, it is universally known that the human papillomavirus (HPV) is a necessary agent.[2,3] This virus can be classified into high-risk and low-risk categories according to the probability of causing cervical cancer.[4] Low-risk HPV very rarely causes a severe lesion, but high-risk HPV types have a higher probability of causing cervical cancer.[5] While there are more than 100 types of HPV, types 16 and 18 are globally known to be responsible for approximately 70% of cancer cases.[6] In Colombia, types 16, 31, 18, 33, 45, and 58 have higher prevalence rates among women.[7]

Because of the lack of early detection, these abnormal cells caused by HPV may not be treated sufficiently early, leading to cervical cancer development and possible spread to nearby organs. Establishing effective detection policies can reduce the mortality rate of the disease by 69% to 81% depending on the strategy[8] and can also decrease the incidence rates of cervical cancer, which is of high importance for Latin American public health systems. After Africa, Central and South America currently rank the highest worldwide in incidence and mortality rates of cervical cancer.[9] In Colombia, cervical cancer remains the first cause of cancer mortality and the second cause of cancer incidence among women.[10] Therefore, to identify the morphologic alterations or inflammatory cells, it is important to screen the uterine cervix in appropriate intervals with specialized tests and tools.

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Address correspondence to Raha Akhavan-Tabatabaei, PhD, School of Management, Sabanci University, Istanbul, Turkey; email: akhavan@sabanciuniv.edu.

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Some important diagnostic procedures that are able to detect abnormalities related to cervical cancer are the Papanicolaou test (also called the Pap test), colposcopy, biopsy, endocervical curettage, fast HPV DNA test, and Arbor Vita cervical cancer test, among others.[1,11,12] The most common screening procedure around the world is the Pap test,[13,14] in which cells are scraped off the cervix wall for examination under a microscope,[1,11] due to its relative low cost and reduced invasiveness. The Colombian National Cancer Institute reports a sensitivity of 36.8% and specificity of 99.2% for this test.[15] Colposcopy is a medical procedure that is performed only if it is highly suspicious that the patient has abnormal conditions in the cervical cells. This procedure examines the vagina and cervix using a lighted magnifying instrument called a colposcope[16] in order to identify any abnormalities and grade them. The biopsy is performed only after finding severe abnormalities during the colposcopy, and its result is the grade of the abnormality and requires the removal of tissue for examination under a microscope by a pathologist.[16] The rest of these procedures are not currently practiced in Colombia on a common basis; therefore, we do not consider them in this study.

After these diagnostic procedures, if the cervical cells are completely normal, the patient is considered healthy. Otherwise, according to the severity of the amorphologic or inflammatory condition, the patient is diagnosed with abnormalities such as atypical squamous cells of undetermined significance (ASCUS), HPV, cervical intraepithelial neoplasia (CIN), carcinomas, or cancerous cells.

ASCUS is diagnosed when the abnormal cells from the outer walls of the cervix have mild cellular changes with an unknown cause. For the HPV diagnosis, it is important to identify the virus in terms of low or high risk, since its infection is the principal factor that leads to the development of cancer.[2,3] CIN indicates abnormal cell growth on the surface of the cervix. According to the thickness proportion of the epithelium involved, it is classified with numbers from I to III, where III is the most severe status.[17] CIN is also classified as squamous intraepithelial lesion (SIL) and following the National Cancer Institute's Bethesda System.[14] CIN I is equivalent to low-grade SIL (LSIL), and CIN II or CIN III are equivalent to high-grade SIL (HSIL). In our study, we use the SIL notation. Finally, carcinoma is diagnosed when the cancer has already begun in tissue that covers the cervix. According to the severity of the disease in terms of the size of the impacted tissue and organs affected, the International Federation of Gynecology and Obstetrics[18,19] classifies cervical cancer into stages from I to IV in increasing order of severity. Supplementary Appendix A summarizes the description of these potential diagnoses in a table.

The treatments performed on cervical cancer patients aimed at removing the lesion or preventing the advancement of abnormalities are cauterization, conization, or hysterectomy, depending on the characteristics of the patient and the extent of affected tissue. Cauterization is performed when the affected part is small and superficial and consists of removing the affected tissue, and cauterizing does the same with the exposed tissue. Conization is similar but implies the removal of a larger cone from the cervix, covering most of the affected part. A hysterectomy completely removes the cervix and can be performed only on HSIL or patients with low-level cancer (cases in which cancer has grown locally but not spread to any other part of the body).

When the patient already has cancer in an advanced stage, the recommended treatment is chemotherapy, radiotherapy, or palliative care in the worst case.[20] The first 2 types of treatment consist of killing cancerous cells, chemotherapy with drugs, and radiotherapy with high-energy radiation. Finally, palliative care is given to improve the life quality of patients who have an untreatable form of cancer, taking care of all possible side effects of the disease or of the treatments received. In this article, we do not consider cancer treatment as the objective is cancer prevention. If a patient is diagnosed with cancer, our model stops.

Several models have been proposed to study screening and treatment policies for cervical cancer. Myers and others[21] proposed a Markov model to study the effects of varying natural history parameters on the incidence of cervical cancer. Kulasingam and others[22] designed a decision analysis model based on that of Myers and others[21] to determine the association between the number of colposcopies per life-year gained for different starting ages of screening. They also evaluated screening strategies using HPV DNA testing in conjunction with cytology and compared that with cytology only.[22] Goldie and others[23] studied the cost-effectiveness of screening in HIV-infected women, and Goldie and others[24] analyzed the cost-effectiveness of various screening strategies using population-specific data. Kim and others[25] studied the value of HPV vaccination for boys in addition to girls in low-resource settings, and Goldie and others[26] proposed mathematical models to study the cost-effectiveness of HPV vaccination of young adolescent girls in Latin America and the Caribbean.

Ginsberg and others[27] calculated regional generalized cost-effectiveness estimates of screening, prevention, and treatment in a global and regional analysis. For Latin America, several studies have been developed to characterize HPV and cervical cancer and also study the cost-effectiveness of screening polices. Campos and others[28] studied the frequency of screening in low- and middle-income countries including Nicaragua. They used a Monte Carlo simulation model of the natural history of HPV and cervical cancer to estimate lifetime health and economic outcomes of HPV-DNA screening and cytology at selected age intervals. Gamboa and others[8] compared the cost-effectiveness of conventional cytology and HPV-DNA testing in Colombia using a Markov model. Wiesner-Ceballo and others[29] carried out a community intervention in Soacha (a low-income suburb of Bogota, Colombia) and adopted a cancer control model proposed by the Colombian National Cancer Institute using social strategies founded on human rights bases.

As can be noted, most of the existing literature on cervical cancer screening focuses on cost-effectiveness analysis and generally uses simulation models to characterize the evolution of the disease. However, effective cervical cancer screening policies involve a sequence of decisions to be made in the lifetime of a patient regarding the type and frequency of screening, making it an interesting stochastic and dynamic decision process problem. Schaefer and others[30] promote Markov decision processes (MDPs) as appropriate tools to model and solve such stochastic and dynamic problems. However, to the best of our knowledge, they have never been applied to cervical cancer screening.

The objective of the present study is to identify optimal screening policies for cervical cancer prevention for the Colombian population, according to factors such as age, record of the last screening, and risk of acquiring the different virus types and also the available detection and treatment procedures in this country. To evaluate these policies, we analyze the tradeoffs between the cost of screening and early treatment procedures versus the risk of letting the disease advance. To this end, we propose a finite-horizon MDP model and develop a numerical example based on the information provided by Colsubsidio, a Colombian health management company and the Colombian National Cancer Institute.

Currently, the Ministry of Health in Colombia recommends that all women older than 25 years and those younger than 25 who have already begun their sexual activity repeat the cytology (Pap test) in a ''1-1-3'' scheme. This scheme consists of testing the patients in 2 consecutive years and repeat in 3 years, if the results of the first 2 tests are negative, regardless of their individual risk factors.[13] However, many health care providers, including Colsubsidio, consider the high probability of a patient not returning after 3 years and therefore recommend 1 Pap test per year.

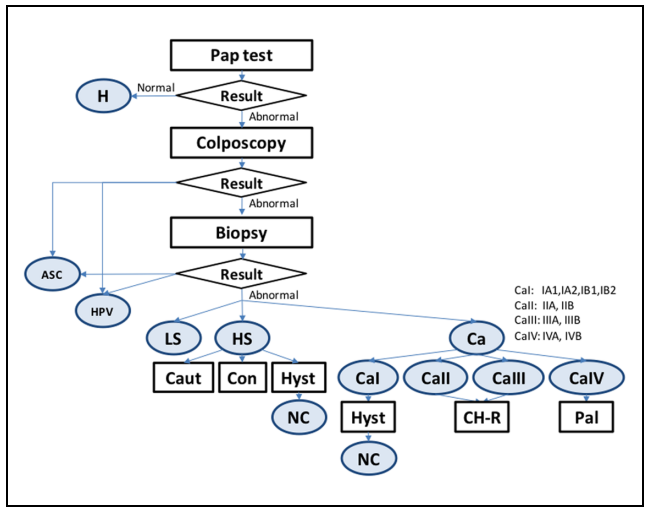

Figure 1 Current practice of Colsubsidio in screening and treatment of cervical cancer patients.

The current screening and treatment practice performed by Colsubsidio on potential and actual cervical cancer patients is shown in Figure 1. In this figure, circles represent the possible diagnosed states of a patient and rectangles show the possible treatments that a patient can receive for each diagnosed state and her individual status (age and HPV risk).

The remainder of this article is organized as follows. In the next section, we present the components and construction of the MDP model along with its assumptions and present a numerical example case study, using sample data from Colsubsidio. Finally, in the Discussion section, we provide some conclusions and a discussion of possible future work.

PROPOSED MDP MODEL

In this section, we first describe the assumptions made in the MDP model and then present its main components, including the transition probabilities. Then we show how to estimate these probabilities

based on the age of the patient and her type of HPV infection. Further, we illustrate the construction of our proposed model and discuss the solution procedure adopted to solve it. Finally, we present numerical results by applying the model to the data from Colsubsidio.

Model Assumptions

We base our model assumptions mainly on a series of interviews with obstetric-gynecologic physicians on their common practice. Note that these physicians visit only Colsubsidio-affiliated patients with private health insurance. Initially, we assume that each patient (who holds private health insurance) receives her annual Pap test, regardless of her age or other factors. In addition to this regular screening, the proposed model in this study considers the decisions of repeating the Pap test, performing a colposcopy directly without a preceding Pap test, or taking no action, 6 months after the required annual test. Note that we do not consider a direct biopsy as part of our decision space, since it is mandatory to perform after abnormal colposcopy outcomes and cannot be performed without prior colposcopy results in Colombia.

The direct colposcopy decision is taken only if there is a very high suspicion of disease progression, based on previous cytology or other test results (e.g., consecutive positive Pap results). This test compared with the Pap test has some intuitive advantages because the lesion can be accurately diagnosed and the treatments can be given in a more timely fashion, avoiding the cost of advanced stages of the disease. The health care provider can also have financial benefits from skipping the Pap test as it eliminates the probability of the patient not returning to a second visit to perform the colposcopy after an abnormal Pap test outcome. Furthermore, a direct colposcopy circumvents the possibility that the patient will not return after an abnormal Pap test and thus addresses patient adherence and compliance issues that arise in screening policies. The disadvantages include higher costs and difficulty of performing the procedure.[31]

The ''do nothing'' (DN) decision occurs when neither a Pap test nor colposcopy is performed in the 6-month interval between required annual Pap tests. It involves a higher probability of missing a possible diagnosis of a risky patient. This could allow advancement of the disease, which in the future will imply higher costs. Hence, our model should analyze the tradeoffs of the above-mentioned actions, knowing the involved costs, advantages and disadvantages, and the risk of letting the disease advance naturally.

Our model does not include the decision problem arising after a patient is diagnosed with cancer, as our goal is to prevent the patients from reaching this state. However, it does consider the cost of required treatments if the patient advances to HSIL or cancer. According to the colposcopy or biopsy outcomes, it is necessary to perform the respective treatment to remove the affected cells. Therefore, we assume the average costs of the mandatory treatments that are performed based on the health status of the patient without providing specific treatment decisions.

We make several assumptions for our model based on practical reality and also for simplification: 1) For the DN decision, high-grade lesion or cancer stages progress or stay at the same level but never regress without treatment. 2) The HPV risk of a patient never changes in only 1 decision epoch, because this risk is related to the type of virus, and a patient needs to be relieved from 1 type in order to acquire the other. 3) All screening tests are considered to be 100% accurate, with complete sensitivity and specificity. Although this assumption is limiting, in the absence of accurate data for the specificity and sensitivity of screening tests in Colombia, the model could still produce useful guidelines on the frequency of screenings. While the less than perfect accuracy and precision of the tests are well known, to our knowledge no studies have been performed to actually quantify these shortcomings. However, by assuming a 100% sensitivity and specificity, we expect the model to produce more frequent false alarms and type II errors where the presence of HPV or suspicious cells goes undetected. Furthermore, it is well known in statistical process control that the only way to simultaneously improve the frequency of both type I and II errors is to increase the sample size and/or frequency. With the results of our model suggesting testing twice per year, this increased frequency helps to overcome the deficiency in the tests. Moreover, these assumptions will lead to overly conservative policies, which will further minimize patient risk.

While we assume that the Pap tests are perfect, our modeling approach does allow us to capture the essence of a false-positive via the colposcopy procedure. The results of the colposcopy may be either normal or abnormal. The normal outcome does not

Table 1 Definition of State Variables

State → X: {s, a, z}												
s	Patient diagnosis	Healthy	ASCUS	Low-risk HPV	High-risk HPV	Low-risk LSIL	High-risk LSIL	HSIL	Cancer	No cervix	Dead	No info
	Notation	H	ASC	HPV_LR	HPV_HR	LS_LR	LS_HR	HS	CA	NC	DEAD	NOI
a	Age, y	From 15 to 65+										
z	Record of last screening test	1	The patient has received her last screening in the last decision epoch.									
		0	The patient has not received her last screening in the last decision epoch.									

Note: ASCUS = atypical squamous cells of undetermined significance; HPV = human papillomavirus.

mean that the patient is 100% free of abnormalities, only that no further action needs to be taken. ASCUS (ASC) is one of the 3 possible normal outcomes. The ASC state denotes atypical squamous cells of undetermined significance, which may be completely benign. This is the line we walk to simultaneously say that the Pap test is ''perfect''; thus, at least some abnormality exists, and capturing the concept false-positives by allowing that the abnormality to be very minor and insignificant. The essence of a false-negative is also being captured, as false-negatives would lead to higher incidences of screened patients having abnormal and possibly advanced abnormal health states. The model would seek to overcome these false-negatives by prescribing more frequent screening.

Model Components

We define the decision epoch as every 6 months and a finite decision horizon of 100 years, with 200 decision epochs, taking into account that the youngest women in the model are 15 years old. It is also assumed that all test and treatment procedures following a Pap or direct colposcopy will be completed within the decision epoch. If the patient is diagnosed with cancer during this period, the treatment will of course continue, but once diagnosed with cancer, the patient exits our model.

The state space is defined with 3 variables that describe the principal aspects of a patient's profile. The first variable s corresponds to the current diagnosis of the patient including information about her risk related to the HPV type or LSIL, if applicable. Note from Table 1 that the HPV and LSIL states are denoted with the extension of either LR (low risk) or HR (high risk) depending on the type of infection. The second variable a represents the age of the patient. Risk profiles are inherently incorporated into age as women have higher probabilities of contracting HPV at different ages. The last variable z is binary and takes into account whether or not a screening test has been performed in the last decision epoch. This variable allows the model to understand whether a Pap test is required or optional for the given decision epoch. Table 1 describes the notation and all possible values that each of these variables can take on.

The set of actions include ''do nothing'' or DN, ''Pap test'' or P, and ''colposcopy without Pap test,'' denoted by C. Note that Action DN implies no action in between 2 consecutive annual Pap tests, Action P on patients with $z = 1$ implies a second Pap test in that year, and Action C implies a colposcopy in mid-year between 2 annual Pap tests.

Regarding the transition probabilities, in the present literature the majority of the information is presented for age range intervals of 5 years beginning from 15 years old,[8,13,32] and therefore we keep the same convention. To estimate these probabilities, we use the data set provided by Colsubsidio and other sources, taking into account the age of the patient and the HPV type.

Regarding the costs, we formulate a value function considering not only the immediate costs of taking the action but also the intangible cost of maintaining a patient for the decision epoch in a certain state using a life-quality index[33] as well as the future expected costs according to the possible transitions based on the actions taken.

Estimating the Transition Probabilities

The transition probabilities are calculated taking into account all the possible transitions from a specific state. Figure 2 shows the transition rate diagram of the underlying Markov chain. In this figure, within 1 observation period, a healthy woman (H) can transition to be diagnosed with ASCUS (ASC), low-risk HPV (HPV_LR), high-risk HPV (HPV_HR),

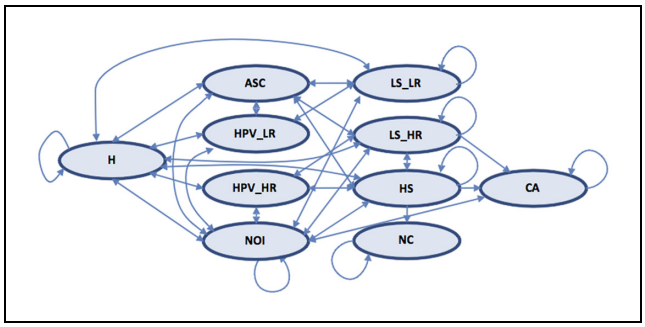

Figure 2 Transition rate diagram for the Markov decision process where H = healthy, ASC = ASCUS, HPV_LR/HR = low-/high-risk HPV, NOI = no information, LS_LR/HR = low-/high-risk LSIL, HS = HSIL; NC = no cervix, and CA = cancer.

low-risk LSIL (LS_LR), high-risk LSIL (LS_HR), HSIL (HS), or simply not adhere to the periodic screening recommendation, in which case the system loses information on her (NOI). Only a patient already diagnosed with high-risk LSIL, HSIL, or with no diagnosis due to failure in adherence (NOI) can develop cancer within one transition period. Also a patient in the states of cancer or HS can undergo hysterectomy and be classified with no cervix (NC) within 1 period. This model is constructed based on the following medical considerations regarding the progression and regression of the disease: 1) CIN or SIL occur only in presence of the HPV[34]; 2) LSIL is equivalent to CIN I or II, and HSIL is equivalent to CIN III[35]; 3) HSIL exists only in the presence of HPV_HR[34]; 4) only lesions related to HPV_HR can progress to cancer[36]; 5) lesions related to HPV_LR do not progress into cancer[36]; 6) once the cancer develops, the disease does not regress without intervention by treatment.[35]As the objective of our model is to prevent cancer, once a patient reaches the cancer state, the model has no further purpose and is concluded. Thus, cancer is considered an absorbing state in our model.

Regarding the decision DN, we use information provided by Gamboa and others[8] on the natural progression of cervical cancer in Colombian women. For the other 2 decisions, namely P and C, Colsubsidio provides information from their patient database.

At the time of this study, Colsubsidio had 122,107 female patients 15 years or older, with gynecological information. To estimate the transition probabilities from this database, we took a random sample of this population. Barnett[37] proposes a sampling method for subpopulations that present a specific property, shown in Equation 1.

$$\boldsymbol{n} = \frac{N\varphi^2 pq}{[e^2(N-1)]+[\varphi^2 pq]} \quad (1)$$

In Equation 1, N denotes the total size of the population; e corresponds to the desired confidence level, which in our study is assumed 95%. Variable κ is the risk of not obtaining the specified confidence level from the sample size. It is drawn from a standard normal distribution, which is equal to 1.96 for 95% confidence. Also, p is the proportion of individuals who exhibit the property of interest in the population. In our case, this property is the population of each 5-year age range. Variable q is the complementary probability of p ($q = 1 - p$). Finally, n corresponds to the final sample size for each age range. Sample size calculations for each age range in our case study are presented in Table 2. Given our data set, this formula suggests the collection of at least 957 samples of patients, and we work with a slightly larger sample of 1141 patients.

Moreover, transition probabilities also consider the age of health information, which is tracked with element z of the state space (see Table 1). Information is newer and thus more accurate if a Pap test was performed in the past 6 months (i.e., $z = 1$). As noted previously, the z variable also tells the model whether a Pap test is required or optional for the given decision epoch.

MDP Model Formulation

The MDP formulation finds the set of policies that minimize costs across a finite horizon. We formulate a value function that represents the behavior of the cervical health states according to the action taken, including immediate and future costs. Table 3 summarizes the notation used in our MDP formulation.

Figure 3 identifies how the health state of the patient changes according to the action taken. When a Pap test is performed, the outcome is normal with probability P_{pn}, and the patient is considered completely healthy (with state H). On the other hand, if the Pap test shows abnormal results (with probability P_{pw}), the patient must return for a second visit. With probability P_{vn}, the patient does not adhere to the second visit recommendation and is classified as no information (NOI), taking into account that the model cannot track the abnormality found. If the patient comes back to the system and receives a colposcopy, this could have normal or abnormal results with probabilities P_{cn} or P_{cw}, respectively (assuming colposcopy to be a perfect test). If the result is normal, the patient could still

Table 2 Sample Size Calculations Based on Age Range

Age Range (y)	Population Size (n)	Proportion according to Total Population Size, p (%)	Minimum Suggested Sample Size (n)	Size of Collected Sample
15–19	5854	4.794	49	56
20–24	15,912	13.031	121	147
25–29	17,074	13.983	129	148
30–34	14,700	12.039	113	160
35–39	14,247	11.668	110	134
40–44	14,660	12.006	113	127
45–49	13,329	10.916	104	117
50–54	9806	8.031	79	90
55–59	6786	5.557	56	67
60–64	4449	3.644	38	49
65+	5290	4.332	45	46
Total	122,107	100	957	1141

Table 3 Notation Used in the Formulation of the Cost Function

Notation	Description	Details
t	Decision epoch	t = 15, 15.5, 16, . . . , 115
X_t	Represent the diagnosed state at decision moment t	$\{s_t, a_t, z_t\}$ where s is the diagnosed state, a is the age range, and z is the binary variable
s_t	State related to the disease at decision moment t	Healthy (H), ASCUS (ASC), human papillomavirus (HPV) of low- and high-risk (LR and HR), LSIL (LS_LR and LS_HR), HSIL (HS), cancer (CA), no cervix (NC), or no information patient (NOI)
a_t	Age of the patient at decision moment t	Ranges from age of 15 to 65 y and older
z_t	Records if the patient has received the screening test in the last decision moment $(t-1)$	1 if the patient receives screening in the last period and 0 otherwise
BigM	Variable that takes a very high value in the DN action value function. Makes the model avoid this DN decision when $z = 0$.	Force the model to accomplish the mandatory screening test per year
D	Set of decisions, d	Pap test (P) or (1), colposcopy (C) or (2), do nothing (DN) or (3)
g_d	Cost related with the decision taken, d	A different cost for Pap test, colposcopy, biopsy, and for a second visit to the doctor
$k(x_t)$	Cost of treatments received by a patient in some state x	It is different than zero for patients in HSIL and CA because these are the only states that need mandatory treatment after screening test
$h(x_t)$	Intangible cost of maintaining a patient in each state with a certain age at decision moment t	Related to the life-quality of each state
$\boldsymbol{P^d}(\boldsymbol{x_t}, \boldsymbol{x'_{t+0.5}})$	Transition probability under decision d of going from x_t to $x_{t+0.5}$ in 1 decision period	
$U_t(x_t, d)$	Value function that takes into account all immediate and future costs	Our MDP finds the decision that has the minimum total cost in each decision moment and assigns it to $U_t^*(x_t)$
$P_{pn}(x_t)$	Probability of normal results in Pap test according to the health state and age	
$P_{pw}(x_t)$	Probability of abnormal results in Pap test according to the health state and age	$1 - P_{pn}(x_t)$

(continued)

Table 3 (continued)

Notation	Description	Details
$P_{vy}(x_t)$	Probability of return for the second visit according to the health state and age	
$P_{vn}(x_t)$	Probability of not returning for the second visit according to the health state and age	$1 - P_{vy}(x_t)$
$P_{cn}(x_t)$	Probability of normal results in colposcopy according to the health state and age	
$P_{cw}(x_t)$	Probability of abnormal results in colposcopy according to the health state and age	$1 - P_{cn}(x_t)$
$P_{bn}(x_t)$	Probability of normal results in biopsy according to the health state and age	
$P_{bw}(x_t)$	Probability of abnormal results in biopsy according to the health state and age	$1 - P_{bn}(x_t)$

Note: ASCUS = atypical squamous cells of undetermined significance; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion; MDP = Markov decision process.

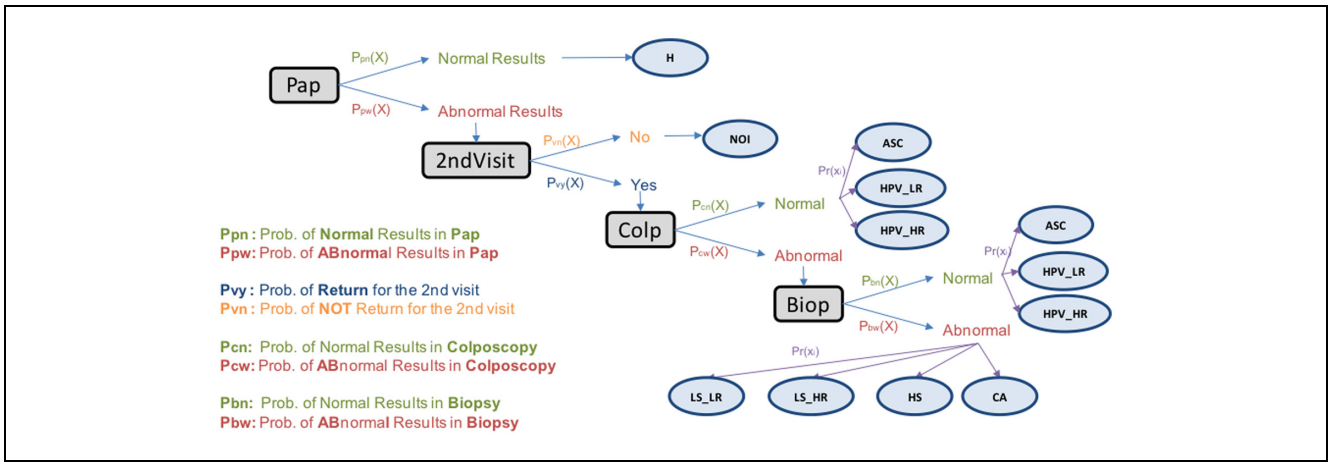

Figure 3 *New initial state according to the screening test results.*

have these abnormalities: ASC, HPV_LR, or HPV_HR, due to her abnormal Pap test outcome. Therefore, after a positive Pap test, it is assumed that there will be some "noncancerous" abnormality prior to the colposcopy. If the colposcopy shows an abnormal outcome, the patient receives a biopsy. The biopsy (also assumed perfect) can present normal results with probability P_{bn}, implying that the patient is noncancerous but not completely healthy either; in fact, with certain probability, the patient could have ASC, HPV_LR, or HPV_HR. Otherwise, if the biopsy shows an abnormal outcome, the patient could have LS_LR, LS_HR, HS, or cancer.

As shown in Table 3, in our formulation, the MDP state variable x_t indicates the state of a patient at time t and $x_{t+0.5}$ her immediate future state, which is defined after the screening test results are revealed (after 6 months). For example, if the patient is believed to be healthy ($x_t = H$) and we select decision P, her next state will be revealed from the results of the Pap test. Thus, if the Pap test turns out to be abnormal and the colposcopy results show HPV_LR, the transition probabilities are estimated from this last state ($x_{t+0.5}$ = HPV_LR).

Furthermore, Figure 3 graphically shows the steps that comprise the cost functions of the decisions in the value function. We consider the cost of

taking the screening actions (P and C), treatment costs, patient's life-quality loss (Table 4) and the future expected costs. It should be noted that in this article we do not propose a function that relates a specific monetary value to quality of life. We leave this to the decision makers who will be implementing the screening policy. In the numerical example, we will propose a hypothetical function to demonstrate the workings of the model. The cost of treatment and life quality are incurred once the true state $x_{t+0.5}$ is known. Finally, the future expected costs are considered with the transition probabilities beginning in state x_{15}.

All of these considerations are included in the value function, and the objective is to find the policy with the minimum total cost. The general formulation is presented in Equation 2, where $U_t^*(x_t)$ is the minimum expected cost at time t given the current state (x_t) and choosing from the set of feasible decisions for x_t, $d \in D_{X_t}$. With this definition, $U_t(x_t)$ is also interpreted as the value function at epoch t, given the state x_t. In Equations 3, 4, and 5, we present how the cost function at time t, denoted by $U_t(x_t)$ changes according to actions DN, P and C, respectively.

$$U_t^*(x_t) = \min_{d \in D_{X_t}} \{U_t(x_t)\} \ \forall t, x_t \tag{2}$$

Specifically, in the value function, the immediate cost includes the cost of the treatments performed in each state and the costs related with the action taken, as well as an intangible cost related to the life quality of a patient in each state. The future cost involves the optimal value function of the states to which it is possible to transition in the next decision epoch, beginning at a specific state. The notation used in the following set of equations is explained in Table 3.

$$U_t(x_t, DN) = BigM * (1 - z) + k(x_t) + h(x_t) + \left(\sum_{x' \in X_t} P^{DN}_{x_t, x_{t+0.5}} * U^*_{t+0.5}(x_{t+0.5} | a_{t+0.5}) \right) \tag{3}$$

$$\begin{aligned}
U_t(x_t,P) = {} & g_p + P_{pn}(x_t) \left\{ k(x_{t+0.5} | x_{t+0.5} = (H,1)) + h(x_{t+0.5}) + \left(\sum_{x_{t+1} \in X_t} P^P_{x_{t+0.5}, x_{t+1}} * U^*_{t+1}(x_{t+1} | a_{t+1}) \right) \right\} \\
& + P_{vn}(x_t) \left[k(x_{t+0.5} | x_{t+0.5} = (NOI,1)) + h(x_{t+0.5}) + \left(\sum_{x_{t+1} \in X_t} P^P_{x_{t+0.5}, x_{t+1}} * U^*_{t+1}(x_{t+1} | a_{t+0.5}) \right) \right] \\
& + P_{pw}(x_t) \left\{ + P_{vy}(x_t) \left[g_C + g_2 + P_{cn}(x_t) \left(\sum_{x_{t+0.5} = \left\{ \begin{array}{l} (ASC,1), \\ (HPV_L,1), \\ (HPV_H,1) \end{array} \right.} P(x_{t+0.5}) \left[k(x_{t+0.5}) + h(x_{t+0.5}) + \left(\sum_{x_{t+1} \in X_t} P^P_{x_{t+0.5}, x_{t+1}} * U^*_{t+1}(x_{t+1} | a_{t+0.5}) \right) \right] \right) \right. \right. \\
& \left. \left. P_{cw}(x_t) \left(g_b + P_{bn}(x_t) \left[\sum_{x_{t+0.5} = \left\{ \begin{array}{l} (ASC,1), \\ (HPV_L,1), \\ (HPV_H,1) \end{array} \right.} P(x_{t+0.5}) \left[k(x_{t+0.5}) + h(x_{t+0.5}) + \left(\sum_{x_{t+1} \in X_t} P^P_{x_{t+0.5}, x_{t+1}} * U^*_{t+1}(x_{t+1} | a_{t+0.5}) \right) \right] \right] \right. \right. \right. \\
& \left. \left. \left. + P_{bw}(x_t) \left[\sum_{x_{t+0.5} = \left\{ \begin{array}{l} (LS_L,1), \\ (LS_H,1), \\ (HS,1), \\ (CA,1) \end{array} \right.} P(x_{t+0.5}) \left[k(x_{t+0.5}) + h(x_{t+0.5}) + \left(\sum_{x_{t+1} \in X_t} P^P_{x_{t+0.5}, x_{t+1}} * U^*_{t+1}(x_{t+1} | a_{t+0.5}) \right) \right] \right] \right) \right] \right\}
\end{aligned} \tag{4}$$

Table 4 Life Quality Associated with Each Health State and Age Range

Health State\Age (y)	15	20	25	30	35	40	45	50	55	60	65
H	0.93000	0.91000	0.91000	0.91000	0.89000	0.89000	0.86000	0.86000	0.80000	0.80000	0.74000
ASC	0.85560	0.83720	0.83720	0.83720	0.81880	0.81880	0.79120	0.79120	0.73600	0.73600	0.68080
HPV_LR	0.69750	0.68250	0.68250	0.68250	0.66750	0.66750	0.64500	0.64500	0.60000	0.60000	0.55500
HPV_HR	0.69750	0.68250	0.68250	0.68250	0.66750	0.66750	0.64500	0.64500	0.60000	0.60000	0.55500
LSIL_LR	0.76260	0.74620	0.74620	0.74620	0.72980	0.72980	0.70520	0.70520	0.65600	0.65600	0.60680
LSIL_HR	0.76260	0.74620	0.74620	0.74620	0.72980	0.72980	0.70520	0.70520	0.65600	0.65600	0.60680
HSIL	0.74400	0.72800	0.72800	0.72800	0.71200	0.71200	0.68800	0.68800	0.64000	0.64000	0.59200
NC	0.65100	0.63700	0.63700	0.63700	0.62300	0.62300	0.60200	0.60200	0.56000	0.56000	0.51800
NOI	0.58590	0.57330	0.57330	0.57330	0.56070	0.56070	0.54180	0.54180	0.50400	0.50400	0.46620
CA	0.51026	0.49929	0.49929	0.49929	0.48832	0.48832	0.47186	0.47186	0.43894	0.43894	0.40602
Dead	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000

$$U_t(x_t,C)=g_C+P_{cn}(x_t)\left(\sum_{x'_t=\left\{\begin{array}{l}(H,1),\\(ASC,1),\\(HPV_L,1),\\(HPV_H,1)\end{array}\right\}} P(x_{t+0.5})\left[k(x_{t+0.5})+h(x_{t+0.5})+\left(\sum_{x_{t+1}\in X_t} P^C_{x_{t+0.5},x_{t+1}} * U^*_{t+1}(x_{t+1}|a_{t+0.5})\right)\right]\right)$$
$$+P_{cw}(x_t)\left(g_b+P_{bn}(x_t)\left[\sum_{x_{t+0.5}=\left\{\begin{array}{l}(ASC,1),\\(HPV_L,1),\\(HPV_H,1)\end{array}\right\}} P(x_{t+0.5})\left[k(x_{t+0.5})+h(x_{t+0.5})+\left(\sum_{x_{t+1}\in X_t} P^C_{x_{t+0.5},x_{t+1}} * U^*_{t+1}(x_{t+1}|a_{t+0.5})\right)\right]\right]\right.$$
$$\left.+P_{bw}(x_t)\left[\sum_{x_{t+0.5}=\left\{\begin{array}{l}(LS_L,1),\\(LS_H,1),\\(HS,1)\\(CA,1)\end{array}\right\}} P(x_{t+0.5})\left[k(x_{t+0.5})+h(x_{t+0.5})+\left(\sum_{x_{t+1}\in X_t} P^C_{x_{t+0.5},x_{t+1}} * U^*_{t+1}(x_{t+1}|a_{t+0.5})\right)\right]\right]\right) \quad (5)$$

Equation 3 represents the reward (or cost) function of the DN action. A BigM formulation is used to ensure that a Pap test is performed at least once a year by making the DN cost prohibitively high if one has not been performed within the past year. The DN cost is the sum of the treatment costs $k(xt)$ and intangible (quality of life) costs $h(x_t)$ for that decision epoch for a patient starting in state x plus

Table 5 Treatment Costs according to the State of the Patient Estimated by Colsubsidio

State	Description	Treatment Cost ($US)
HS	HSIL	$360.00
CA	Cancer	$3,086.00

Table 6 Action-Dependent Costs from Colsubsidio

Notation	Description	Value ($US)
G_p	Pap test	$6.34
g_c	Colposcopy	$45.61
G_b	Biopsy	$90.34
g_2	Second doctor visit	$10.00

the expected future costs given in parentheses and are weighted by the various transition probabilities.

Equation 4 presents the cost function for performing a Pap test. The first term g_p is simply the cost of performing a Pap. The second term represents the treatment cost. Note that the treatment cost contains many nested functions that correspond to the various outcomes of the Pap test and those that may follow. The first path corresponds to a negative (n) Pap test (probability $P_{pn}(x_t)$) in which the model incurs treatment and intangible costs for state x plus the expected future costs. The second path corresponds to a positive (w) Pap test (probability $P_{pw}(x_t)$). A positive Pap test dictates that the patient should return for a colposcopy. However, not all patients will adhere to this policy. Therefore, there is a probability P_{vn} that the patient does not return and then will transition to the ''no information'' (NOI) state. If the patient does return, they will receive a colposcopy at cost g_c plus the cost of the second visit g_2. There are then probabilities associated with either a positive or negative colposcopy, which then may necessitate a biopsy at cost g_b. Likewise, a biopsy has probabilities, based on the health state of the patient, of having a positive or negative outcome and associated costs for each.

Equation 5 is similar in form to that of Equation 4 but begins by performing a colposcopy directly without a prior Pap test.

Tangible costs are obtained from Colsubsidio's current costs of screening and treatment in Colombia. Cost of treatment in our model only takes on values greater than zero for HSIL and cancer states, as they are the only diagnosed states for which the patients receive a treatment. They are calculated as the average of the treatment costs in each of these 2 states, as shown in Table 5. The action-related costs are presented in Table 6 and consider not only the cost of doing a Pap test and colposcopy but also other possible future tests that may be incurred because of a positive test result such as a biopsy and the cost of returning for a second visit. Note that there is no associated cost with the DN decision because it implies that no action was taken.

We tackle intangible costs with the life quality related to each health state. The life quality is calculated according to the symptoms of every health state, and each life quality lost point is associated with a tangible cost. The first step is to find the quality of life associated with all symptoms related to each state using the Health and Activity Limitation Index (HALex).[33] Then, we adapt these qualities according to the average life quality of each age range, found on the same index. This was done by reducing the quality of life value by the corresponding percentage reduction due to age as found in Goldie and others.[23] Table 4 demonstrates the life quality associated with each state and age range. In this scale, value 1 is assigned to a perfectly healthy state and 0 to the worst state, death. The life quality loss is calculated as 1 minus the life quality for each state.

The second step to calculate the intangible costs is to multiply a fixed cost by the life quality lost in each single state of our model, to translate the life quality to a tangible cost that can be compared with the other costs mentioned above. For illustration, suppose we want to calculate the intangible cost of a 30-year-old woman with HPV_HR. According to Table 4, this woman has a quality of life index of 0.68250. Moreover, suppose that fixed cost per life quality loss is $50,000. This yields an intangible cost of $50,000(1 − 0.68250) = $15,875. We recognize that the attribution of a monetary value to a health/age state is very subjective and controversial and something we do not attempt to promote in this work. Rather, we leave the estimation of this value to individual governmental agencies and insurance companies. We use representative values for illustrative purposes for our numerical examples later in this article. This analysis is similar to some cost-effectiveness studies mentioned in references 8, 38, and 39 with the difference that they are based on quality-adjusted life-years, calculated by multiplying the life quality by the life expectancy of a

specific state. However, for the Colombian population, there are no studies that analyze the life expectancy according to the age and the diagnosis of the health state related to cervical cancer, and information from other geographical locations may skew the results.

Solution Procedure

According to Puterman,[40] the backward induction algorithm provides an efficient method for solving finite horizon MDPs. This algorithm gives the optimal solution and does not require high computational efforts, since not all of the variables from each decision epoch need to be recorded because they are summarized through $U^*_{x_t,d_t}$ and $d^*_{x_t}$. The optimal policy for all possible t is the action that attains the minimum value, and its value is given by the optimality equation associated to that action.

Numerical Example Case Study and Analysis

To construct a numerical example using the data and information presented above, some further assumptions are made. In this work, we use a large Colombian health insurance agency as a case study. However, as several assumptions are made on our part, we consider this section to be more of a numerical example rather than a prescription for an actual policy to be implemented for Colombia. There are several high-level decisions and assumptions that must be made, and we leave those to the large insurance companies or government agencies. We provide hypothetical values for some of these to demonstrate the functionality of our model and the sensitivity of certain parameters. Furthermore, while we use Colsubsideo as our motivating case study, we aim to create a model that may be easily generalized to other health agencies or organizations.

We assume the normal outcome in screening tests follows a decreasing probability function of the health status while it deteriorates. For example, the probability that the Pap test has a normal outcome for a patient who starts in the system as healthy should be higher than a patient who begins in LSIL. Although reasonable, the challenge for this assumption is to determine by how much this probability should change according to the change in the state. For this analysis, we organize the health states in our model in decreasing order of the life quality as H, ASC, HPV, LS, HS, NC, NOI, cancer, and dead.

We examine the decreasing probability function assumption under 2 extreme scenarios to test the sensitivity of our model to this input. In the first scenario, we consider that when the health state deteriorates 1 step (e.g., from H to ASC), the probability of having a normal Pap outcome decreases by 10%. The second scenario uses 90%, a highly decreasing function for normal outcome probabilities. In this case, the probability of having a normal outcome with 1 step of heath state depreciation (e.g., from H to ASC) decreases by 90%. We refer to the first scenario as the ''10% test'' and to the second as the ''90% test.'' We run our model with both of these scenarios assuming a fixed cost per lost-life-quality point of US$50,000. Results are presented in Tables 7 and 8. These tables are truncated since the age range when the optimal policy remains constant (i.e., age 65).

Comparing Table 7 and Table 8 shows reasonable differences. In Table 7 (the ''10% test'') for the majority of ages and health states, the Pap test is recommended twice a year, and in the riskier health states and more critical age ranges (15–30 and 45–55), a direct colposcopy is recommended. The DN action is recommended for only healthy patients younger than 65 years. This is reasonable since given the low cost of the Pap test and even considering the intangible costs related to life quality, the model tries to avoid colposcopies as much as possible. Therefore, in most of the cases, it is necessary to perform the Pap test twice per year to prevent the progression of disease to advanced stages going unnoticed.

However, in Table 8, with a high probability of having abnormal outcomes in the screening tests (i.e., the ''90% test''), it is not necessary to perform the Pap test frequently on advanced patients, for whom a high percentage are likely to show abnormal results and therefore require a subsequent colposcopy anyway. Instead, a direct colposcopy is recommended for these patient.

In conclusion, compared with the current government recommendations and Colsubsidio practice, the optimal policies of our model suggest more frequent screening in most of the cases. This can intuitively be interpreted as more frequent screening, leading to more effective prevention programs. Considering only the tangible costs, a decreased frequency of screening is expected. However, taking into account the costs of loss of life quality, performing more frequent screenings is recommended because the immediate and tangible procedure costs are justified by the savings in the intangible cost of

Table 7 Optimal Policy Assuming Probabilities of Having Normal Screening Outcomes Reduced by 10% as the Life Quality of Health State Decreases

Optimal Actions to take for each state and each decision moment

AGE	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	Policy cost
H, 0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 12,544.3215
H, 1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	1	$ 12,537.2560
ASC, 0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 12,546.5813
ASC, 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 12,546.5813
HPV_L, 0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 12,552.4723
HPV_L, 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 12,552.4723
HPV_H, 0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 12,555.8309
HPV_H, 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 12,555.8309
LS_H, 0	2	2	2	2	2	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 12,567.7210
LS_H, 1	2	2	2	2	2	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 12,567.7210
LS_L, 0	2	2	2	2	2	1	1	1	2	1	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	$ 12,569.4561
LS_L, 1	2	2	2	2	2	1	1	1	2	1	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	$ 12,569.4561
HS, 0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	$ 12,571.3399
HS, 1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	$ 12,571.3399
NC, 1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	$ 12,572.4309
NOI, 0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	$ 12,573.3432
CA, 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 12,558.5508
Policy Cost																																																				$ 226,094.3048

1 Pap test 2 Colposcopy 3 Do nothing

Table 8 Optimal Policy Assuming Probabilities of Having Normal Screening Outcomes Reduced by 90% as the Life Quality of Health State Decreases

Optimal Actions to take for each state and each decision moment

AGE	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	Policy cost
H, 0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 15,297.0912
H, 1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	1	1	1	1	1	1	$ 15,289.9144
ASC, 0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 15,304.5495
ASC, 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 15,304.5495
HPV_L, 0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 15,313.2116
HPV_L, 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 15,313.2116
HPV_H, 0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	2	$ 15,336.6098
HPV_H, 1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	$ 15,334.3382
LS_H, 0	2	2	2	2	2	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	$ 15,332.1711
LS_H, 1	2	2	2	2	2	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	$ 15,332.1711
LS_L, 0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	$ 15,336.8464
LS_L, 1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	$ 15,336.8464
HS, 0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	$ 15,334.4726
HS, 1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	$ 15,334.4726
NC, 1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	$ 15,336.8465
NOI, 0	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	$ 15,336.8465
CA, 1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	$ 15,317.4031
Policy Cost																																																				$ 275,828.3988

1 Pap test 2 Colposcopy 3 Do nothing

loss of life quality in a long horizon, through early detection and prevention of the disease.

DISCUSSION

We propose a finite-horizon MDP model to find optimal screening policies for cervical cancer prevention. Our results show that this approach is effective considering that cancer can be tracked more effectively with more frequent Pap tests or colposcopy screenings. In general, the results show that optimal decisions consist of doing more frequent Pap tests or colposcopies instead of taking no action, as they prevent rapid advancement of the disease and can reduce costs in the future. We test the model with different assumptions by varying the probabilities of yielding normal outcomes in the screening test, considering that they follow a decreasing function depending on the deterioration of the health state. The tests consist of varying the decreasing probability function between 2 extreme points, 10% and 90%, and finding the associated optimal policy. In general, as the decreasing function of normal outcomes takes a greater value, the colposcopy decision appears more frequently in the final policy.

Specifically, patients in the health states of LS, HS, NC, or NOI need to perform direct colposcopies more frequently. All patients younger than 20 with a health state worse than LS need to undergo a colposocopy every 6 months in order to follow up the abnormality found at an early age. Moreover, patients between the age of 45 and 55 who have some type of lesion need to undergo 2 colposcopies per year as, at this age, the incidence of HPV_HR is shown to have a higher peak in Colombia.[7] However, healthy patients younger than 60 who receive their mandatory Pap test do not need to undergo any additional screening tests per year.

In general, our model provides relevant findings considering that we are not only performing timely decisions, as many researchers have explored,[13,41–43] but also including additional decision factors based on the specific profile of each patient. The final decisions are given in terms of which screening test is to be performed (either Pap test or direct colposcopy) and the frequency of performing it according to different patient conditions, such as life quality, age, and risk of acquiring HPV. This is very relevant to practitioners as it gives a clear and simple, state-based decision on whether to perform an additional Pap test (every 6 months instead of every year) or perform a colposcopy directly based on the age and health risk of the patient. Previously, guidelines were given for all women regardless of age or health and did not consider the possibility of a direct colposcopy.

A significant contribution is that we formulate a specific cost function that considers not only the current state of the patient but also the state after the screening test results from where the patient is going to possibly transition into another health state in the next epoch, including immediate and future costs. Our model is general and flexible enough to be easily adapted to other populations by modifying input information of transition probabilities and running the algorithm with new data.

However, the model has several limitations in various aspects. The intangible cost analysis uses HALex for the loss of life quality, an index that is not specifically evaluated for Colombian patients. The values of this index are sensitive to geographical differences between populations in different countries. Another limitation is caused by the transition probabilities related to the HPV risk, since we used data from Muñoz and others,[32] which only assume the age range of the patients and not their health state.

Likewise, it is important to improve the assumption of the probabilities of having normal outcomes in the screening tests with more specific medical information, in order to resemble the reality of the disease behavior and screening effectiveness as much as possible. By doing so, we hope to improve the quality of our results and provide practical and yet effective policies for the health care community in Colombia and Latin America. We believe that with this improvement, it is possible to suggest policies at a national level since the model considers the costs not only from the health providers' perspective but also from the patients' perspective or, in other words, not only the tangible costs for the health provider to provide treatments and screenings but also the intangible cost of life quality for the patient.

Considering the lack of accurate information on the life quality indices in Colombia, we note that having a specific study in life quality of Colombian cervical cancer patients is crucial to perform future work related to this study since that is the most significant cost factor and therefore leads to a significant difference in the resulting policy. Moreover, the model is only as good as the input data that are fed to it. This gives motivation to improve the databases of Colombian patients to consider not only

information such as age and health status but also accurate HPV information. Also, it can be shown that changing the fixed cost of each quality lost point does not cause significant changes in the final policy.

Finally, an important limitation is that we are not considering sensitivity and specificity of the screenings tests. By assuming 100% sensitive screening tests, we are raising the number of false alarms in our model results. This means that following the recommendations of our model results in an overreaction to the presence of HPV and leads to more frequent follow-up testing. On the other hand, the assumption of 100% specific outcomes implies ignoring a proportion of cases in which HPV or other signals are present. This could potentially lead to a higher rate of cancer growth. However, since our model is based on at least 1 mandatory annual test and the probability of having several consecutive type II errors is low, any alarming abnormality can theoretically be caught in time before causing cancer. Relaxing this assumption and including imperfect results of screening requires the application of a partially observable MDP. In this approach, the decision maker is assumed to have no certain information about the state space prior to making a decision, and the transition probabilities must be calculated taking into account the set of possible states that are related to a set of observations and probabilities. We see the gathering of the necessary data and the modification of the model accordingly as the next step in this work.

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