Chapter 10

Markov Modeling

Objectives

Upon completing this chapter, the reader will be able to:

1. Explain when Markov modeling may be useful.
2. List the steps in Markov modeling.
3. Interpret a pictorial representation of a Markov model.
4. Explain the advantages and disadvantages of Markov modeling.

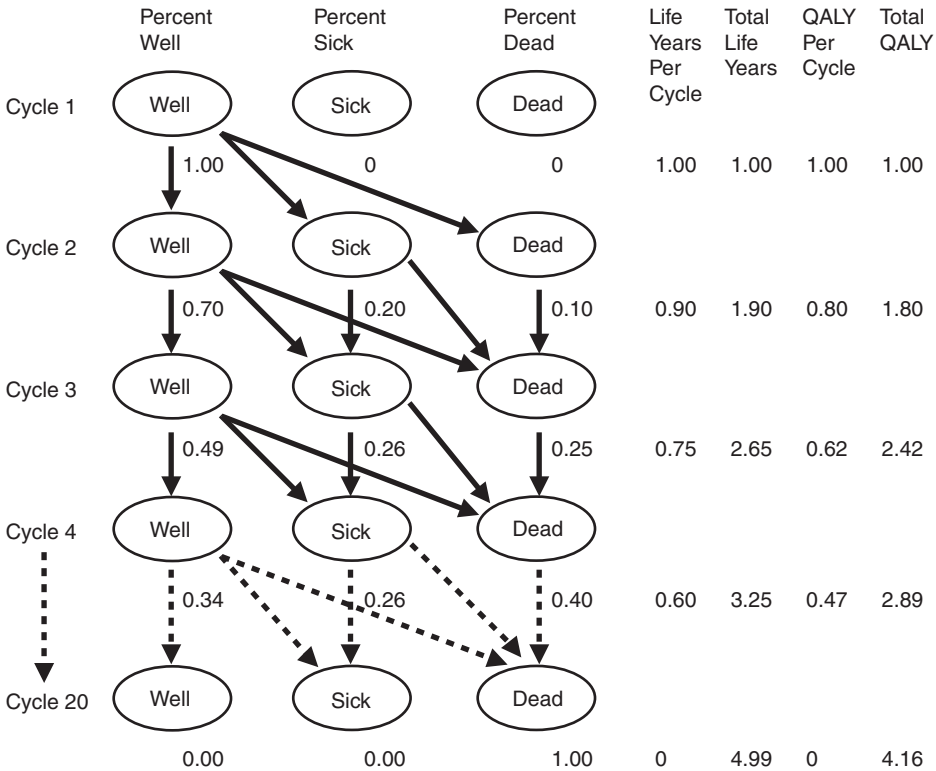
✦ OVERVIEW

In Chapter 9, relatively simple models and short-term health consequences were presented. For many diseases and conditions, more complex outcomes and longer follow-up periods need to be modeled. For these analyses, patients may move back and forth, or **transition,** between **health states** over periods of time.[1–4] For example, a patient who has a blood clot (embolism) may be given a blood thinner (anticoagulant) to reduce the risk of further embolisms. Three possible health states are the patient dies from the embolism, the patient has blood-related problems from the medications (e.g., internal bleeding), or the patient lives with no complications or side effects. Outcomes past this initial health state can be followed further to see whether patients develop future embolisms or future internal bleeding. Each follow-up interval is called a **cycle**, the time period that is determined to be clinically relevant to the specific disease or condition. **Markov analysis** allows for a more accurate presentation of these complex scenarios that occur over a number of cycles, or intervals.

✦ STEPS IN MARKOV MODELING

There are five steps for Markov modeling: (1) choose the health states that represent the possible outcomes from each intervention; (2) determine possible transitions between health states; (3) choose how long each cycle should be and how many cycles will be analyzed; (4) estimate the probabilities associated with moving

(i.e., transitioning) in and out of health states; and (5) estimate the costs and outcomes associated with each option.[1] Each step is discussed in this chapter using a general example (Fig. 10.1) and a more specific diabetes mellitus (DM) example (Fig. 10.2). The DM analysis will model the cost-effectiveness of using a specified diet and exercise plan to increase the length of time that prediabetic patients (impaired glucose tolerance [IGT] is plasma glucose >140 to <200 mg/dL 2 hours after glucose challenge) avoid the transition to DM (plasma glucose >200 mg/dL 2 hours after glucose challenge). For the DM example, patients are followed up for



Example Calculations:

Cycle 1 to Cycle 2

70% of 100% stay well = 70% well
20% of 100% get sick = 20% sick
10% of 100% die = 10% dead

Cycle 2 to Cycle 3

70% of 70% stay well = 49% well
20% of 70% (14%) get sick plus 60% of 20% stay sick (12%) = 26% sick
10% of 70% (7%) die plus 40% of 20% (8%) die + 100% of 10% (10%) stay dead = 25% dead

Cycle 3 to Cycle 4

70% of 49% stay well = 34% well
20% of 49% (10%) get sick plus 60% of 26% (16%) stay sick = 26% sick
10% of 49% (5%) die plus 40% of 26% (10%) die + 100% of 25% stay dead (25%) = 40% dead

QALY Calculations

Cycle 1 = 100% * 1.0 QALY = 1.00 QALY
Cycle 2 = (70% * 1.0 QALY) + 20% (0.5 QALY) + 10% (0 QALY) = 0.80 QALY
Cycle 3 = (49% * 1.0 QALY) + 26% (0.5 QALY) + 25% (0 QALY) = 0.62 QALY
Cycle 4 = (34% * 1.0 QALY) + 26% (0.5 QALY) + 40% (0 QALY) = 0.47 QALY

FIGURE 10.1. Bubble diagram for a general Markov model.

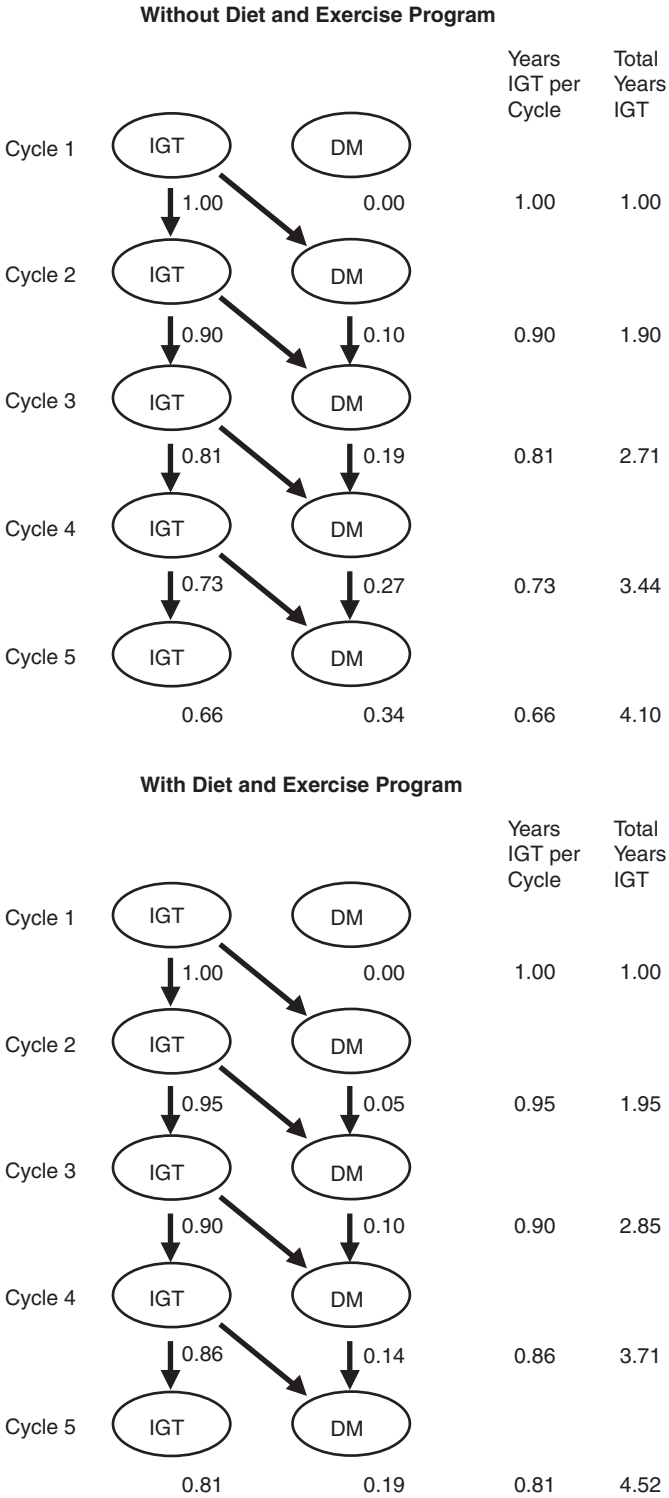


FIGURE 10.2. Bubble diagram for the diabetes example.
IGT = Impared Glucose Tolerance DM = Diabetes Mellitis.

5 years, and it is assumed that none of the patients die during this time frame. The cost of the diet and exercise program is $300 per year. (Estimates and probabilities for this example are used for illustrative purposes only. Published research articles should indicate how these estimates were derived.)

Step 1: Choose Health States

First, a delineation of mutually exclusive health states should be determined by listing different scenarios a patient might reasonably experience. These are referred to as **Markov states.** Patients cannot be in more than one health state during each cycle. A simple general example is "well, sick, or dead." Graphically, by convention, each health state is placed in an oval or circle in a bubble diagram (Fig. 10.1). Time cycles are depicted on the left of the graph. For the DM example, we are concerned with two health states: IGT and DM (Fig. 10.2). A more complex Markov model is illustrated in Example 10.1.

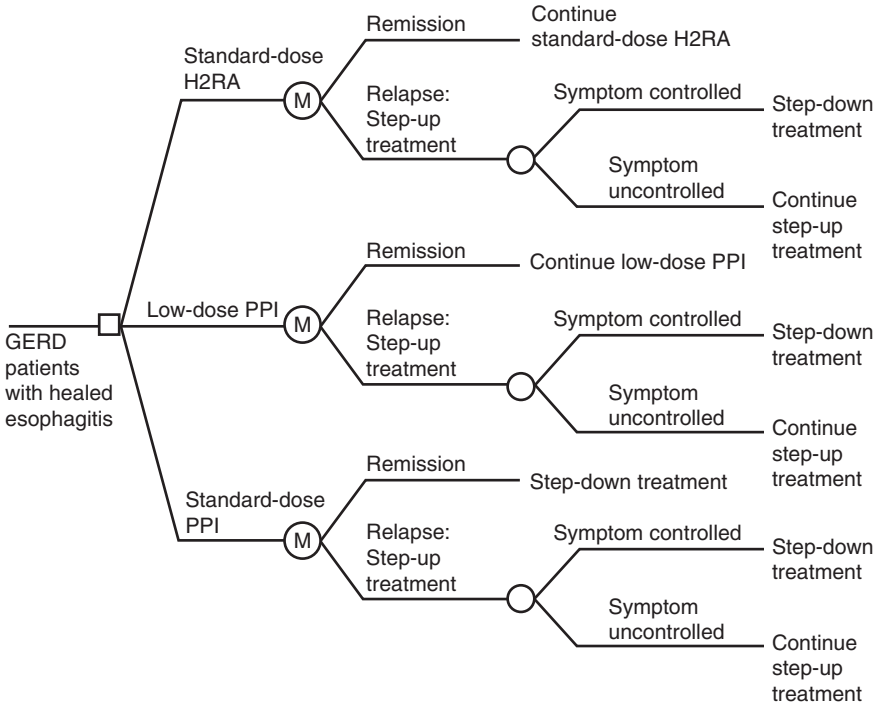
Step 2: Determine Transitions

Next, possible transitions between states are determined based on clinical information. Can patients move (i.e., transition) from one health state to another? For example, if the patient dies, this is called an **absorbing state.** An absorbing state indicates that patients cannot move to another health state in a later cycle. Graphically, arrows are used to indicate which transitions are allowed. In the general example given in Figure 10.1, we assume that everyone starts out in the well state. For cycle 1, each patient can stay well, or can move to the sick or dead states. For the next cycle, patients in the well state can again stay well or move to the sick or dead states. Those in the dead state cannot move back to the other two states. Depending on the disease of interest, patients may or may not be able to move back to the well state after being in the sick state. For example, if a patient gets sick from an infection, it is likely that he or she can recover and become well. If the patient contracts AIDS, he or she may be able to prevent some symptoms or prolong his or her life with medication, but the person would not move back to the well state. For the diabetes example, we will assume that if a patient transitions from the prediabetic state to DM that he or she cannot return to the prediabetic state. Thus, in the diabetes Markov model (Fig. 10.2), DM is an absorbing state.

EXAMPLE 10.1 SUMMARY OF MARKOV MODEL FOR MAINTENANCE TREATMENT FOR GASTROESOPHAGEAL REFLUX DISEASE

Below is a Markov model developed to estimate costs and outcomes associated with 1 year of treatment of gastroesophageal reflux disease (GERD). GERD is characterized by recurrent heartburn and regurgitation (hence the term reflux) and may permanently damage the lining of the esophagus. Both histamine-2 receptor agonists (H2RAs) and proton pump inhibitors (PPIs) are used to treat this disease. In most cases, PPIs are more expensive than H2RAs, so after GERD patients are in remission (no symptoms), lower cost treatments may be used for maintenance therapy.

The authors chose to compare three options for continued therapy: standard-dose H2RAs, low-dose PPIs, and standard-dose PPIs. The nodes with an M inside a circle indicate that a Markov analysis is being used. In this case, the model was run for 12 cycles of monthly treatment.



Step-up treatment: Standard-dose H2RA or Low-dose PPI → Standard-dose PPI → High-dose PPI → 24-hour pH monitoring, duodenoscopy, surgery evaluation

Step-down treatment: High-dose PPI → Standard-dose PPI → Low-dose PPI → Standard-dose H2RA

This example and figure are adapted with permission from You JH, Lee AC, Wong SC, Chan FK. Low-dose or standard-dose proton pump inhibitors for maintenance therapy of gastroesophageal reflux disease: A cost-effectiveness analysis. *Alimentary Pharmacology and Therapeutics* 17(6):785–792, 2003. Used with permission of Blackwell Publishing.

Step 3: Choose the Cycle Length and Number of Cycles

The cycle length depends on the disease being modeled. For the example of patients with a blood clot given in the first paragraph of the chapter, a cycle of 1 week might be enough time to determine the number of patients with additional blood clots or bleeding. For chronic diseases, a cycle length of 1 year is commonly used. Again, the number of cycles depends on clinical relevance. Sometimes the model is run for the natural lifetime of the patients or until a certain percent of the cohort is

in the absorbing state. For the general example (Fig. 10.1), the model was run until there was no one left in the well or sick health states (20 cycles). For the diabetes example (Fig. 10.2), five 1-year cycles were used to determine the impact of the diet and exercise program on progression to diabetes.

Step 4: Estimate Transition Probabilities

Transition probabilities are used to estimate the percent of patients who are likely to move from one health state to another during each cycle. These probability values usually come from previous research or expert panel estimates. For the general example, the transition probabilities are given in Table 10.1. This matrix of transition probabilities contains zeros when patients are not allowed to move from one state to another. For the diabetes example, estimates were used for those with and without the diet and exercise program. For patients who did not receive the specific diet and exercise program, there was a 10% probability per year (cycle) that they would transition from IGT to DM (90% would stay in the IGT state). For patients who received the program, the probability of DM was reduced to 5% per year (95% would stay in the IGT state). It was assumed that after patients were diagnosed with DM, they could not transition back to IGT. Figure 10.3 shows a different method to depict the general Markov model and includes these probabilities for each arrow that links the health state transitions. Figures 10.4 and 10.5 include the probabilities for the diabetes example.

Step 5: Calculate Costs and Outcomes

Outcomes for each health state should be estimated and given a value. If the outcome of interest is years of life gained or saved and each cycle is for 1 year, then each person who is alive during a cycle gets a value of 1.0 as his or her outcome for that cycle. It is common to adjust each year of life in each cycle for the quality of health that year. In Figure 10.1, for each year in a well state, the value is 1.0, and for each year in the sick state, the value is 0.5, and the value for the dead state is 0. Costs in each health state should be estimated as with simple decision analyses. The total costs and outcomes are then summed for all cycles. Figure 10.2 shows that the 5-year diet and exercise program corresponds with an extra 0.42 years (about 5 months) of being in the IGT state before being diagnosed with DM (4.52 years versus 4.10 years in IGT). The additional costs for patients in the program are $300 per year or $1,500 for 5 years if costs are not discounted. The 5-year cost estimate would be $1,415 if discounted using a 3% **discount rate.** This calculates

TABLE 10.1. **TRANSITION PROBABILITIES PER CYCLE FOR GENERAL EXAMPLE**

	To Health State			
	Well	*Sick*	*Dead*	*Total Per Cycle*
From Health State				
Well	0.70	0.20	0.10	1.00
Sick	0.00	0.60	0.40	1.00
Dead	0.00	0.00	1.00	1.00

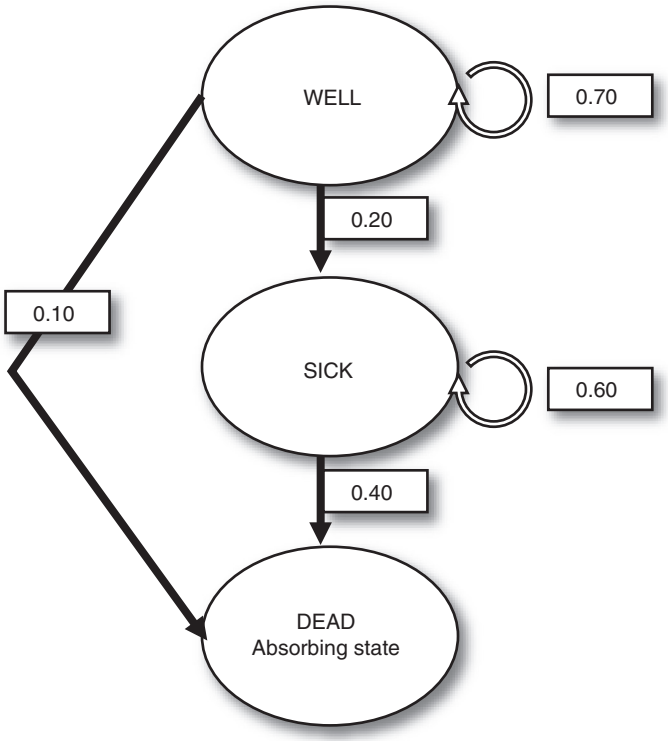
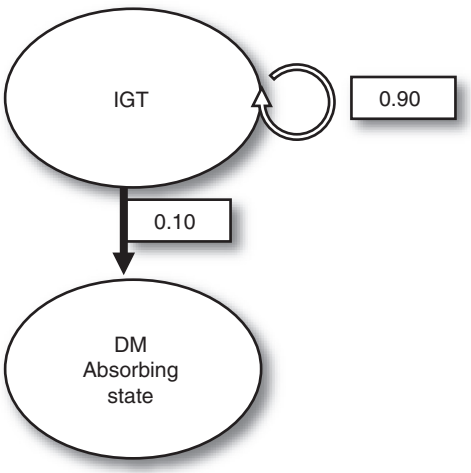
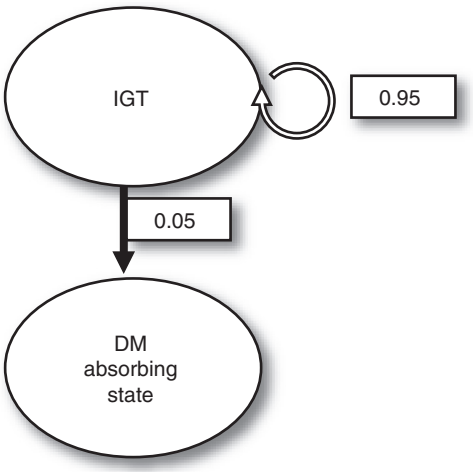


FIGURE 10.3. Alternate representation of a Markov model for the general example.



Model and transition probabilities without diet and exercise program

FIGURE 10.4. Alternate representation of a Markov model for the diabetes example without the diet and exercise program.



Model and transition probabilities with diet and exercise program

FIGURE 10.5. Alternate representation of a Markov model for the diabetes example with the diet and exercise program.

to about $3,571 incremental cost for an extra year without DM ($1,500/0.42 years) if costs are not discounted or $3,369 if discounting is conducted ($1,415/0.42 years). As mentioned in Chapter 5 on cost-effectiveness analysis, there is no consensus on whether or not to discount outcomes (in this example, years without DM). Therefore, some researchers may discount outcomes as well as costs in this analysis. The costs of treating patients with DM would be included for both options in a more complete model. Computer software helps with more complex calculations.

✦ DISADVANTAGES OF MARKOV MODELING

By their nature, Markov models can be more complex than simple decision trees and therefore less **transparent** to decision makers. Researchers strive to strike a balance between developing models that are more complex but better able to capture the true nature of the disease state and developing simpler models that are easier to interpret but may not include important clinical factors.

A commonly cited disadvantage of Markov modeling is that it is "memoryless" because the **Markovian assumption** is that the probability of moving from state to state is not based on the previous experiences from former cycles. In practice, a patient's medical history is an important determinant in the probability of his or her future health. More advanced and complex computations, such as using **tunnel states,** allow for integration of health experiences from previous cycles.[4,5] Another disadvantage is that the data needed to estimate probabilities and costs, especially in the long term, are often unavailable. Most clinical studies measure outcomes for a short time, and extrapolation into the future may compound errors in estimations.

✦ ADVANCED ISSUES

An overview of some advanced issues related to Markov modeling is included in this section. Some advanced topics are addressed in more depth elsewhere (see "References" and "Suggested Readings" sections).

Constant Versus Variable Transition Probabilities

For the examples given in this chapter, it was assumed that the probability of transitioning from one Markov state to another was constant over time from cycle to cycle. A **Markov chain** model is used for constant probabilities. However, this may not be consistent with the information that is known about a disease process. For example, the probability of staying asymptomatic may be 90% per year for the first 5 years of a disease and then may decrease to 80% per year for the next 5 years. Also, if the model extends out over a long period, the cohort "ages," and higher mortality rates from aging should be taken into account for future cycles. Time-dependent **Markov process** models can incorporate changes in probabilities for each cycle by incorporating data from a reference table that lists the probabilities for each cycle based on more realistic clinical information.

Calculation Methods

The two basic calculation methods used to determine the results of a Markov analysis are cohort simulation and Monte Carlo simulation.

Cohort Simulation

Cohort simulation uses a hypothetical group (cohort) of patients that usually start out in the same health state. At each cycle, the transition probabilities are applied. (Probabilities may be the same for every cycle if using a Markov chain analysis, or they may vary by cycle if using a Markov process analysis.) The number of patients in each cycle is calculated and summed using matrix algebra. This type of calculation can incorporate discount rates to account for time value associated with costs and outcomes. The composite article for this chapter uses a cohort simulation technique and incorporates discount rates. Cohort simulation models (as well as the **decision analysis** models in Chapter 9) are referred to as **deterministic** analyses. This means that probabilities and costs are set (predetermined) numbers, and variability (i.e., **uncertainty**) in these numbers is not taken into account. Therefore, for a specific model, the analysis always gives the same numerical results.

Monte Carlo Simulation

Monte Carlo simulation is a type of **stochastic** analysis that takes into account uncertainty or variability at the patient level. A random patient is sent through the model, and outcomes and costs are calculated individually for that patient. Then one by one, more random patients are sent through the model. The path through the model that each patient may take is different because of random variation, and results for a specific model can result in different answers each time the simulation is conducted because of the randomness at chance nodes in the model. If a large number of patients (e.g., 100,000) are sent through the model one at a time, the results may be close to the results of the cohort simulation.

First-order Monte Carlo simulation (sometimes called microsimulation or individual simulation) is used to take into account the patient-level variability seen in medical practice. Second-order simulation deals with uncertainty of the statistical parameters (versus uncertainty at the patient level). This may be referred to as probabilistic sensitivity analysis and is beyond the scope of this book. Explanations and examples can be found elsewhere.[6]

Half-Cycle Corrections

The basic Markov models illustrated so far assume that patients stay in one health state for the entire cycle (e.g., 1 year) and transition at the end of each cycle. In reality, patients move between health states in a continuous fashion over each cycle rather than all transitioning at the end of the cycle. In the diabetes example, everyone was given credit for a whole year in the IGT health state for the first cycle before some patients transitioned to DM. In reality, some of these patients would have transitioned to DM before the 1-year mark. Researchers adjust for this potential overestimation of costs and outcomes by using a **half-cycle correction** which moves patients between beginning and ending cycles at the halfway mark. Mathematically, this is accomplished by dividing the costs and outcomes in the first and last cycle by 2.

✦ OTHER ADVANCED TOPICS

Scatterplots and Cost-Effectiveness Acceptability Curves (CEACs)

As shown in Chapter 5, the incremental costs and incremental effects can be represented visually using the four quadrants of the **cost-effectiveness plane.** The horizontal axis divides the plane according to incremental costs (positive above, negative below) and the vertical axis divides the plane according to incremental effects (positive to the right, negative to the left). Previous examples of incremental cost-effectiveness ratios (ICERs) used "point estimates" of both costs and effectiveness measures, without regard to how these points might vary. Using point estimates, there would be one point on the CE plane to illustrate the ICER between two alternatives. Using one point to illustrate each difference in estimates does not take into account any uncertainty in the measurement, or estimates, of costs or effects. Due to imprecise information on the effectiveness of and the resources consumed, both the costs and effects of health interventions are associated with some degree of uncertainty. One method that is typically used to represent the uncertainty in the costs and effects associated with a treatment is a scatter plot of simulated (by bootstrapping or probabilistic modeling) incremental cost and effect pairs on the incremental cost-effectiveness plane. In an example comparing Statin A and Statin B, the point estimate of differences in costs was calculated to be $5,000 higher for Statin A than for Statin B; and the point estimate of differences in effect was calculated to be 0.13 QALY higher for Statin A than for Statin B; which would result in a ICER of $5,000/0.13 = $38,462 per additional QALY. A scatterplot of joint comparisons of potential differences in costs and effects (i.e., plot of cost-effect pairs) for different theoretical patients based on variations (uncertainty) of these variables is illustrated in Figure 10.6. The cost differences range from −$300 (savings of $300 for Statin A) to about $10,000. The effect differences range from

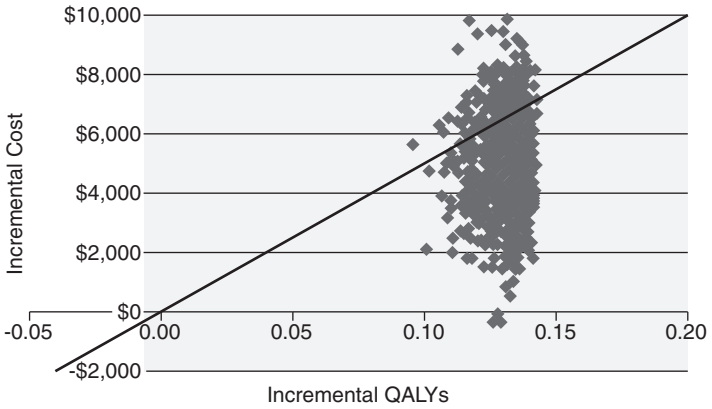


FIGURE 10.6. Scatterplot. Statin A versus Statin B.

0.10 to 0.14 additional QALYs for Statin A compared to Statin B. Over 95% of the points from the cost-effect pairs fall in quadrant I (northeast), indicating that Statin A is more costly and more effective for these points. For the few points that fall in quadrant II (southeast), these paired comparisons show Statin A is less costly and more effective (i.e., dominant). The next question is to determine the probability that the added value is worth the added cost. The angled straight line (ray) in Figure 10.6 indicates where the ICER is $50,000 per QALY (a commonly used threshold or ceiling ratio). To calculate the probability that Statin A is cost-effective compared with Statin B, the proportion of the scatter plot points that fall to the south and east of the ray is determined. In this example the probability (proportion) is 82% that Statin A is cost-effective at the threshold of $50,000. Since the maximum acceptable ceiling ratio, or threshold, is not always stated, (and a standard has not been agreed upon), a sensitivity analysis should be undertaken. This is accomplished by using a cost-effectiveness acceptability curve (CEAC). This curve is constructed by plotting the proportion of the incremental cost-effect pairs that are cost-effective for a range of threshold or ceiling values. Figure 10.7 illustrates the CEAC for the Statin example. As mentioned, at the ceiling of $50,000, 82% of the points are in the cost-effective range. If the maximum threshold was reduced to $35,000/QALY (ray angle moves down and right) the proportion of cost-effect points decreases to 41%, whereas if the ceiling is raised to $65,000/QALY (ray angle increases up and to the left) the proportion increases to 96%. Note that if a QALY is valued at $100,000 the probability of cost-effectiveness of Statin A calculated using joint ratios is 100% (all points would fall below the ray).

SUMMARY

Markov analysis provides a method of adding a time component to decision analyses and is useful when modeling health events that can occur repeatedly over time. It may be a more realistic representation of more complex disease states. Markov modeling can start with clinical (usually short-term) data and incorporate more long-term data from studies of natural disease progression and epidemiology. For a specific research question, the possible health states are defined, the relevant length and number of cycles are determined, transition probabilities between health states are estimated, and both costs and outcomes over a number of cycles

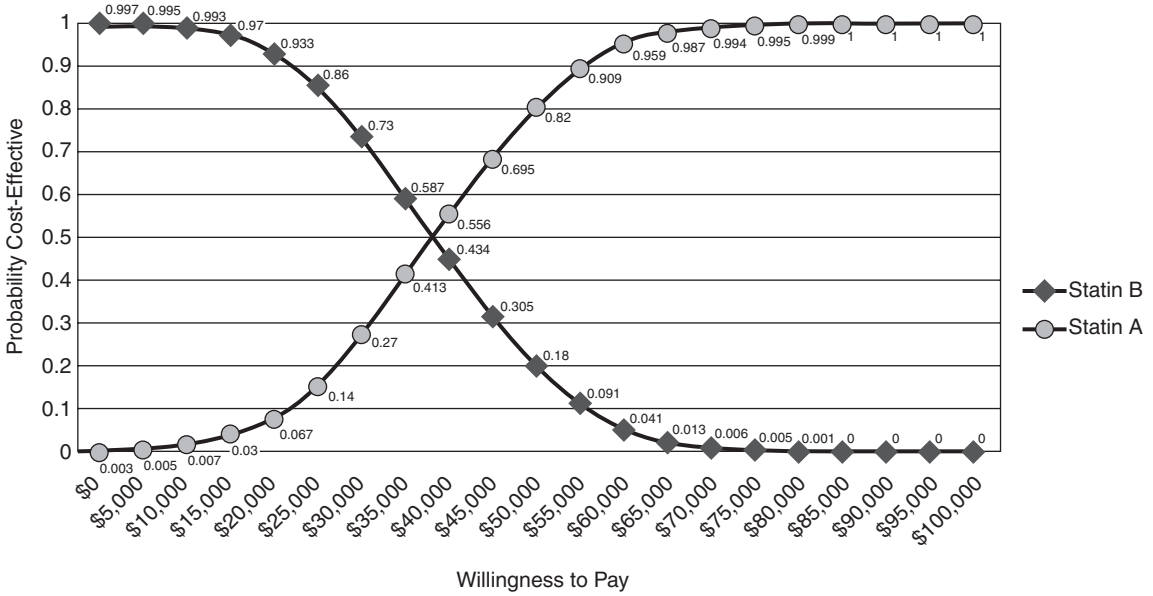


FIGURE 10.7. Cost-effectiveness Acceptability Curve. Statin A versus Statin B.

are calculated and summed. The probabilities of transitioning from one state to another may be held constant over time **(Markov chain analysis)** or may differ depending on the cycle **(Markov process analysis).** A limitation of Markov modeling is the assumption that the probability of moving from state to state is not dependent on previous health states the patient may have experienced, which may not be a realistic depiction for some research questions. More advanced (but more complex) analyses have been used to address this limitation.

COMPOSITE ARTICLE 1: MARKOV MODELING—INITIATION OF HIV THERAPY

Note: Haesuk Park, a PhD student, helped develop this composite article.
More information about this topic can be found in the following references:
Athan E, O'Brien DP, Legood R. Cost-effectiveness of routine and low-cost CD4 T-cell count compared with WHO clinical staging of HIV to guide initiation of antiretroviral therapy in resource-limited settings. AIDS *24:1887–1895, 2010.*
Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.
World Health Organization (WHO). HIV/AIDS Programme. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Available at http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf

Title: COST-EFFECTIVENESS OF TWO METHODS TO GUIDE INITIATION OF ANTIRETROVIRAL THERAPY IN SUB-SAHARAN AFRICA

INTRODUCTION: It was estimated that 22.5 million adults and children live with Human immunodeficiency virus (HIV) in sub-Saharan Africa. One indication of the impact of having this virus can be measured by determining the level of CD4 cells in a patient's blood sample.

If CD4 cells become depleted, the patient is left vulnerable to a wide range of infections. In the developed countries, highly active antiretroviral therapy (ART) in the late 1990s brought significant improvement in the quantity and quality of life for patients with HIV. The results of randomized controlled trials and several observational cohort studies demonstrated that ART can reduce transmission of HIV and is a cost-effective intervention. The Department of Health and Human Services Panel recommends ART for patients with CD4 counts ≤500 cells/mm^3 ("strong" recommendation for CD4 counts <350 cells/mm^3 and "moderate" recommendation for CD4 counts 350 to 500 cells/mm^3). In developing countries, the initiation of ART is guided by the patient's CD4 cell count (some treat if ≤200 cells/mm^3, others when the count gets ≤350 cells/mm^3 or less). Where reliable CD4 cell count testing is not available, the World Health Organization (WHO) has developed clinical staging guidelines for the initiation of ART. Symptomatic stage 3 (advanced immunosuppression) and stage 4 (severe symptoms/AIDS) indicate the need to start ART. The objective of this study was to develop a Markov model of HIV infection and compared the direct health care costs and benefits in life years or quality-adjusted life years (QALYs) gained using two methods to assess the need to start ART: (1) routine CD4 cell count versus (2) WHO clinical staging of HIV. The incremental cost-effectiveness ratios (ICERs) in US dollars per life year (LY) and quality-adjusted life year (QALY) were estimated from the perspective of the public health services in a sub-Saharan African setting.

WHO clinical staging of established HIV infection

HIV-Associated Symptoms	WHO Clinical Stage
Asymptomatic	1
Mild symptoms	2
Advanced symptoms	3
Severe symptoms	4

METHODS: A Markov state transition probability model, following a hypothetical cohort of 10,000 HIV-infected individuals starting with a CD4 cell count more than 350 cells/mm^3, was developed comparing the two approaches to guide initiation of ART (Exhibits 10.1 and 10.2). The Markov model was constructed in Microsoft Excel to estimate the total direct medical costs, patients' life expectancy, and quality of life for the two options. Three health states were used in the model: (1) CD4 cell count of 350/mm^3 or more (no treatment), (2) CD4 cell count of 200 or less or WHO stage 3 or 4 (AIDS) (treatment with ART), and (3) death. Patients in the model were reviewed

EXHIBIT 10.1

Markov Model 4 Count

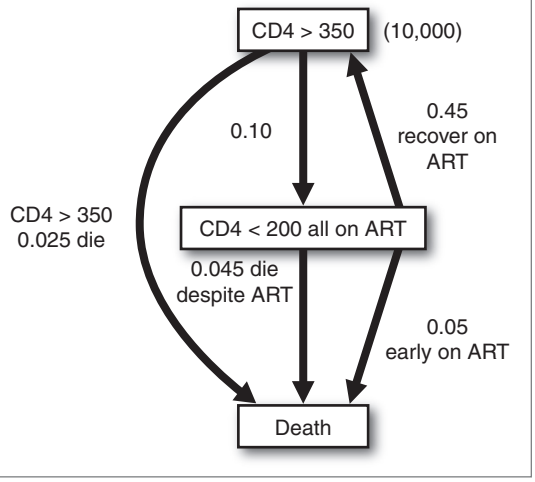
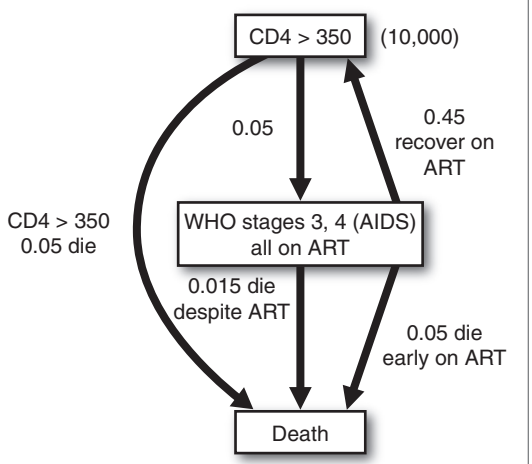


EXHIBIT 10.2

Markov Model—WHO Staging



annually for consideration of ART by either CD4 cell count of 200 mm^3 or less or by WHO stage 3 or 4 criteria. It is possible that patients who receive ART could go back to the state of CD4 cell count more than 350 mm^3. A portion of patients would progress despite commencement of ART. The transition probabilities were based on published studies and are listed in Exhibit 10.3. The costs of treating HIV patients include the costs of providing ART and other direct health care treatment costs such as treating opportunistic infections, and monitoring and treating adverse effects of therapy. The costs of first-line and second-line ART are derived from published studies in developing countries. All costs used in the model were reported in 2008 US dollars. These estimates appear in Exhibit 10.4. In the base case analysis, future costs and outcomes were discounted at 3% per annum as recommended in a developing country setting. Twenty 1-year cycles were modeled. Sensitivity analyses were conducted for costs, time horizon and the discount rate. The cost-effectiveness threshold used in this analysis is based on an ICER per QALY gained below the per capita gross domestic product (GDP) for the Republic of South Africa ($9,800) and Cote d'Ivoire ($1,700). (See Exhibit 10.5 for model and calculations.)

EXHIBIT 10.3

Transition Probabilities

CD4 Cell Testing to Guide Antiretroviral Therapy	
CD4 > 350 → CD4 < 200	10.00%
CD4 > 350 → death	2.50%
CD4 < 200 → CD4 > 350 recover on ART	45.00%
CD4 < 200 → die early on ART	5.00%
CD4 < 200 → die despite ART	4.50%
WHO Staging 3, 4 (AIDS) to Guide Antiretroviral Therapy	
CD4 > 350 → WHO stages 3, 4 (AIDS)	5.00%
CD4 > 350 → death	5.00%
WHO stages 3, 4 (AIDS) → CD4 > 350 recover on ART	45.00%
WHO stages 3, 4 (AIDS) → die early on ART	5.00%
WHO stages 3, 4 (AIDS) → die despite ART	1.50%

EXHIBIT 10.4

Costs, Health Care Utilization, and Utilities

Costs (per year)	
CD4 cell test routine	$15
Drug cost	
ART first-line	$300
ART second-line	$680
Health care cost	
Inpatient	$180
Outpatient	$30
Health care Utilization (per year)	
Inpatient visits	
CD4 cell count > 350	4.0
CD4 cell count ≤ 200	1.0
AIDS	2.0
Outpatient visits	
CD4 cell count > 350	3.0
CD4 cell count ≤ 200	9.0
AIDS	8.0
Utilities	
CD4 cell count > 350	0.890
CD4 cell count < 200	0.830
AIDS	0.730

RESULTS: Exhibit 10.6 shows that for baseline calculations, the total costs and effects, in terms of life years (LYs) and QALYs for individuals assessed by WHO staging criteria were $8,710, 10.46 LYs, and 9.17 QALYs, respectively. For those individuals assessed by annual routine CD4 cell count testing, the costs, LYs, and QALYs were $10,013, 11.87 LYs, and 10.46 QALYs, respectively. With these estimates, the ICER of CD4 cell count testing compared with the WHO clinical staging was $923 per life year gained and $1008 per QALY gained. Sensitivity analysis (Exhibit 10.7) shows this result to be robust to the ranges given because the highest

EXHIBIT 10.5

Calculations of the Markov Model

A. Data Markov Analysis: CD4 Cell Count Testing

Markov State				Outcome		Cost			
Cycle	CD4 > 350	CD4 < 200 all on ART	Death	Life Years	QALYs	CD4 Cell Test Routine ($)	ART Cost ($)	Health Care Cost (Inpatient and Outpatient) ($)	Total Cost (CD4 Cell Test +ART+ Health Care Costs) ($)
0	10,000	0	0	10,000	8,900	150,000	0	8,100,000	8,250,000
1	8,750	1,000	250	9,466	8,367	141,990	475,728	7,317,961	7,935,680
2	8,106	1,330	564	8,895	7,841	133,419	614,290	6,753,287	7,500,996
3	7,691	1,416	893	8,334	7,340	125,016	634,861	6,284,450	7,044,327
4	7,367	1,413	1,220	7,801	6,868	117,020	615,303	5,867,013	6,599,336
5	7,082	1,380	1,538	7,299	6,425	109,491	583,201	5,484,046	6,176,738
6	6,818	1,336	1,846	6,829	6,010	102,431	548,260	5,128,481	5,779,172
7	6,567	1,290	2,143	6,388	5,622	95,821	513,826	4,796,826	5,406,473
8	6,326	1,243	2,430	5,976	5,259	89,635	480,993	4,486,923	5,057,552
9	6,095	1,198	2,706	5,590	4,920	83,848	450,060	4,197,150	4,731,058
10	5,873	1,155	2,973	5,229	4,602	78,435	421,044	3,926,130	4,425,609
11	5,658	1,113	3,229	4,891	4,305	73,370	393,874	3,672,624	4,139,869
12	5,452	1,072	3,476	4,576	4,027	68,633	368,448	3,435,492	3,872,574
13	5,253	1,033	3,715	4,280	3,767	64,202	344,661	3,213,672	3,622,535
14	5,061	995	3,944	4,004	3,524	60,056	322,408	3,006,175	3,388,640
15	4,876	959	4,165	3,745	3,296	56,179	301,591	2,812,076	3,169,846
16	4,698	924	4,378	3,503	3,084	52,551	282,119	2,630,510	2,965,180
17	4,527	890	4,583	3,277	2,884	49,158	263,903	2,460,666	2,773,728
18	4,361	858	4,781	3,066	2,698	45,984	246,864	2,301,789	2,594,637
19	4,202	826	4,971	2,868	2,524	43,015	230,925	2,153,170	2,427,110
20	4,049	796	5,155	2,683	2,361	40,238	216,015	2,014,147	2,270,399
			Per patient	11.870	10.463	178	831	9,004	10,013

B. Data Markov Analysis: WHO Staging

Markov State				Outcome		Cost			
Cycle	CD4 > 350	WHO Stages 3, 4 (AIDS)	Death	Life Years	QALYs	No Testing ($)	ART Cost ($)	Health Care Cost (Inpatient and Outpatient) ($)	Total Cost (ART+ Health Care Cost) ($)
0	10,000	0	0	10,000	8,900	0	0	8,100,000	8,100,000
1	9,000	500	500	9,223	8,131	0	237,864	7,368,932	7,606,796
2	8,325	695	980	8,502	7,462	0	321,001	6,749,222	7,070,223

(continued)

B. Data Markov Analysis: WHO Staging *(Continued)*

Markov State				Outcome		Cost			
Cycle	CD4 > 350	WHO Stages 3, 4 (AIDS)	Death	Life Years	QALYs	No Testing ($)	ART Cost ($)	Health Care Cost (Inpatient and Outpatient) ($)	Total Cost (ART+ Health Care Cost) ($)
3	7,805	757	1,438	7,835	6,863	0	339,364	6,201,304	6,540,668
4	7,365	761	1,874	7,220	6,318	0	331,349	5,706,341	6,037,691
5	6,971	741	2,288	6,653	5,819	0	313,289	5,254,523	5,567,812
6	6,608	712	2,681	6,130	5,360	0	292,079	4,840,038	5,132,117
7	6,267	679	3,054	5,648	4,938	0	270,580	4,458,917	4,729,497
8	5,946	646	3,408	5,204	4,550	0	249,933	4,108,092	4,358,025
9	5,642	614	3,744	4,795	4,192	0	230,551	3,784,993	4,015,544
10	5,354	583	4,063	4,418	3,862	0	212,539	3,487,358	3,699,897
11	5,081	553	4,365	4,070	3,559	0	195,878	3,213,150	3,409,028
12	4,822	525	4,653	3,750	3,279	0	180,498	2,960,512	3,141,010
13	4,576	498	4,925	3,456	3,021	0	166,316	2,727,742	2,894,058
14	4,343	473	5,184	3,184	2,784	0	153,243	2,513,276	2,666,519
15	4,121	449	5,430	2,934	2,565	0	141,197	2,315,673	2,456,869
16	3,911	426	5,663	2,703	2,363	0	130,096	2,133,606	2,263,702
17	3,712	404	5,884	2,490	2,177	0	119,868	1,965,854	2,085,722
18	3,523	384	6,094	2,295	2,006	0	110,443	1,811,292	1,921,735
19	3,343	364	6,293	2,114	1,848	0	101,760	1,668,881	1,770,641
20	3,173	346	6,482	1,948	1,703	0	93,759	1,537,668	1,631,427
			Per patient	10.457	9.170	0	419	8,291	8,710

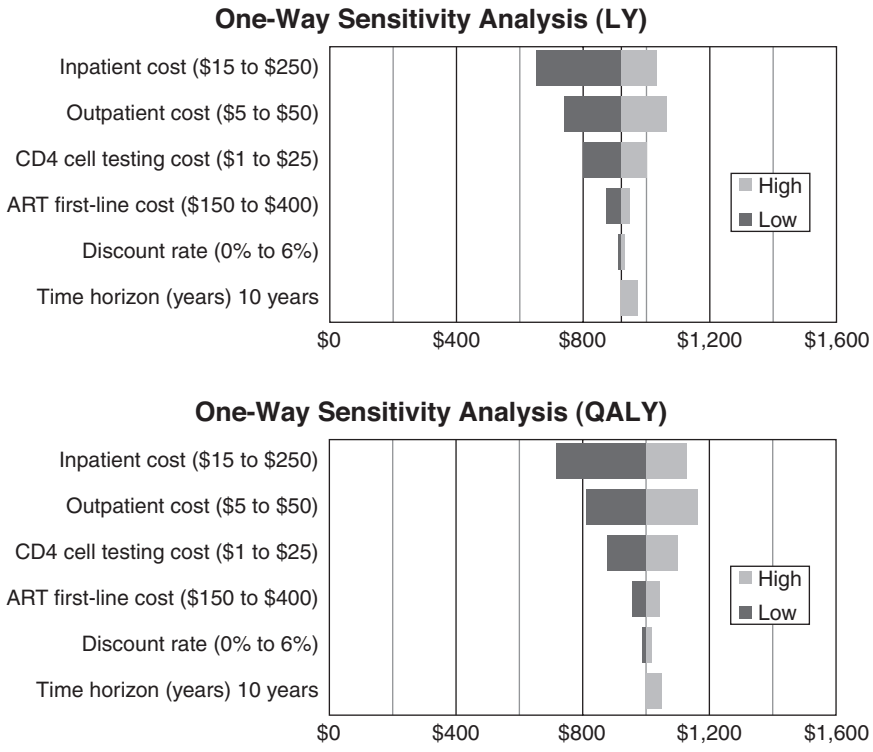
EXHIBIT 10.6

Base Case Costs, Effects, and Cost-Effectiveness of CD4 Cell Testing Compared with WHO Staging to Guide Initiation of Antiretroviral Therapy for HIV-Infected Individuals Over 20 Years

	Costs ($)	Total Life Years	QALYs	Incremental Cost per Life Year Gained (ICER)	Incremental Cost per QALY Gained (ICER)
WHO staging	8,710	10.457	9.170		
Routine CD4 cell testing	10,013	11.870	10.463	$923	$1,008
Cost-Effect Threshold GDP per Capita 2008					
Republic of South Africa					$9,800
Cote D'Ivoire					$1,700

EXHIBIT 10.7

One-Way Deterministic Sensitivity Analysis



incremental cost per QALY gained was $1,165, which is below the threshold value of $1,700.

DISCUSSION AND CONCLUSIONS: Limitations of this study include the assumption of effectiveness of ART. Drug resistance may emerge after 10 years and longer term studies are required. In addition, societal costs were not included. Utilizing routine CD4 cell counts compared to WHO clinical staging in order to guide initiation of ART for patients infected with HIV appears to be a very cost-effective intervention for sub-Saharan Africa. We recommend the implementation of routine CD4 cell testing as an integral part of the scale-up of ART programs in the sub-Saharan African public health services.

WORKSHEET FOR CRITIQUE OF MARKOV COMPOSITE ARTICLE

1. Complete Title?

2. Clear Objective?

3. Appropriate Alternatives?

4. Alternatives Described?

5. Perspective Stated?

6. Type of Study?

7. Relevant Costs?

8. Relevant Outcomes?

9. Adjustment or Discounting?

10. Reasonable Assumptions?

11. Sensitivity Analyses?

12. Limitations Addressed?

13. Generalizations Appropriate?

14. Unbiased Conclusions?

ANSWERS

1. **Complete Title:** Although the title does say the type of study (cost-effectiveness) it does not include what the two options were—CD4 testing versus WHO staging.
2. **Clear Objective:** The objective was clearly stated " ... to develop a Markov model of HIV infection and compared the direct healthcare costs and benefits in life years or quality-adjusted life years (QALYs) gained using two methods to assess the need to start ART."
3. **Appropriate Alternatives:** The authors addressed the two common methods for determining when to start ART and why they were important to compare.
4. **Alternatives Described:** Although the CD4 count assessment was clear with cut-offs, more information could have been given about WHO staging criteria.
5. **Perspective Stated:** The perspective was clearly stated as the "public health services in a sub-Saharan African setting." Thus, only direct medical costs were included.
6. **Type of Study:** The study has been identified as a cost-effectiveness analysis. The outcomes were measured as both life years (LYs) gained—a CEA—and QALYs gained—a CUA. However the CUA is a type of CEA, so the title just including the term CEA is appropriate.
7. **Relevant Costs:** Based on the stated perspective, the direct medical costs of ART and HIV treatment were included.
8. **Relevant Outcomes:** LYs and QALYs are important outcomes in the treatment of HIV since both length and quality of life are affected by the disease and treatment.

9. **Adjustment and Discounting:** All costs were assessed in 2008 US dollars—discounting for the future 20 years was conducted at a rate of 3% (and varied in the sensitivity analysis).
10. **Reasonable Assumptions:** It was assumed that the QALYs values were valid and the probabilities and costs obtained from literature were accurate. It was assumed that the cost-effectiveness threshold would be below the GDP of developing countries.
11. **Sensitivity Analyses:** Sensitivity analyses were conducted by varying the costs, time horizon, and the discount rate. Findings were robust (not sensitive) to these variables/ranges.
12. **Limitations Addressed:** Limitations on long-term effectiveness of ART and that societal costs were not included.
13. **Generalizations Appropriate:** The analysis included input costs and probabilities. A researcher could re-run the analysis with data specific for a different population. The authors did not try to extrapolate beyond sub-Saharan African populations.
14. **Unbiased Conclusions:** The authors do not overstate their results. Based on these numbers and sensitivity analyses, CD4 testing to determine initiation of ART in HIV patients is more effective than using the WHO staging criteria for this population at a reasonable cost.

COMPOSITE ARTICLE 2: MARKOV MODELING—PHOSPHATE BINDERS

Note: Haesuk Park, a PhD student, helped develop this composite article.
More information about this topic can be found in the following references:
Park H, Rascati K, Keith M, Hodgkins P, Smyth M, Goldsmith D, Akehurst R. Cost-effectiveness of lanthanum carbonate versus sevelamer hydrochloride for the treatment of hyperphosphatemia in patients with end-stage renal disease: A US payer perspective. Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research *2011:14(8), 1002–1009.*
Bernard L, Mendelssohn D, Dunn E, Hutchison C, Grima DT. A modeled economic evaluation of sevelamer for treatment of hyperphosphatemia associated with chronic kidney disease among patients on dialysis in the United Kingdom. Journal of Medical Economics 16(1): 1–9, 2013.

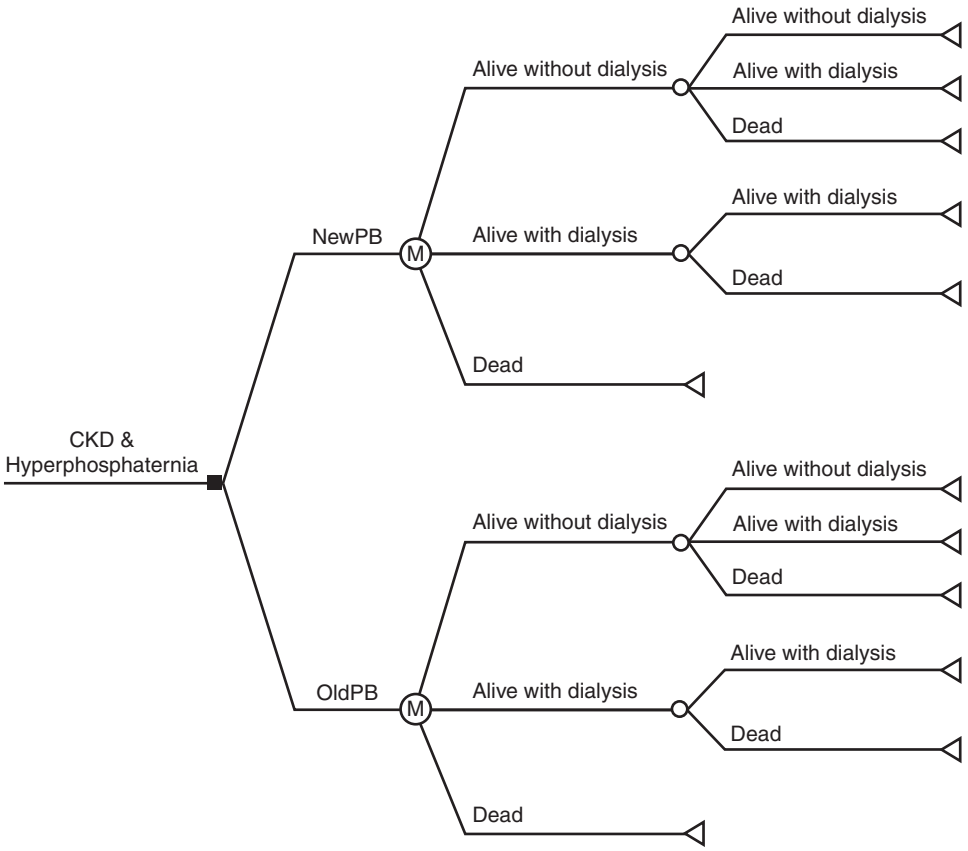
Title: COST-EFFECTIVENESS OF NEW PHOSPHATE BINDER (NEWPB) FOR THE TREATMENT OF HYPERPHOSPHATEMIA IN CHRONIC KIDNEY DISEASE PATIENTS

INTRODUCTION: The clinical and economic burden associated with chronic kidney disease (CKD) is significant. Patients with CKD are at increased risk of premature death and other health issues such as cardiovascular disease and require lifelong care. Hyperphosphatemia (elevated levels of phosphorus in the body) is a common complication of CKD and strongly associated with increased risk of morbidity and mortality in patients with CKD. Phosphate binders (PBs), which lower serum phosphorus level, are a key component in the successful management of hyperphosphatemia. OldPB has been the standard of care for almost 20 years and is relatively inexpensive but has been associated with an increased risk of cardiovascular events and mortality. NewPB was newly introduced to reduce the long-term safety of OldPB but it is more costly. Recently, a randomized, open-label study evaluated NewPB versus OldPB on mortality and the inception of dialysis. The purpose of this study was to assess the cost-effectiveness of NewPB compared with OldPB in patients with CKD from the US payer perspective.

METHODS: A Markov model was built in Excel 2010 to compare the two PBs (NewPB versus OldPB) in patients with CKD and

EXHIBIT 10.8

Markov Model – CKD Example



hyperphosphatemia. Transitions between three relevant clinical states were considered: *alive without dialysis, alive with dialysis* and dead (Exhibit 10.8). In the model, all patients started in alive without dialysis. From this health state, patients could remain in *alive without dialysis* or transit to *alive with dialysis* or progress to dead. Transition probabilities were taken from a randomized clinical trial (Exhibit 10.9). Outcomes for 10 years were extrapolated using regression analysis beyond the duration of the clinical trial (3 years follow-up) for both

EXHIBIT 10.9

Transition Probabilities – CKD Example

Transition Probability	
Alive without dialysis → Alive with dialysis	
NewPB	10.60%
OldPB	17.40%
Alive without dialysis → dead	10.00%
Alive with dialysis → dead	15.00%

EXHIBIT 10.10

Costs and Utilities – CKD Example

Costs (per Year in 2013 US Dollars)		*Probabilistic Sensitivity Assumptions*
Drug		
NewPB	$5,000	gamma
OldPB	$2,000	gamma
Dialysis	$20,000	gamma
Utilities		
Alive without dialysis	0.850	beta
Alive with dialysis	0.720	beta

EXHIBIT 10.11

Calculations of the Markov Model

A. Data Markov Analysis: NewPB

Markov State				*Outcome*		*Cost*		
Cycle	*Nondialysis*	*Dialysis*	*Dead*	*Life Years*	*QALYs*	*Drug Cost*	*Dialysis Cost*	*Total Cost (Drug + Dialysis Costs)*
0	10,000	0	0	10,000	8,500	$52,000,000	$0	$52,000,000
1	7,936	1,064	1,000	8,571	7,154	$44,571,429	$20,261,131	$64,832,559
2	6,298	1,748	1,953	7,299	5,998	$37,953,230	$31,715,984	$69,669,214
3	4,999	2,156	2,845	6,181	5,011	$32,138,666	$37,249,823	$69,388,489
4	3,967	2,364	3,669	5,209	4,175	$27,086,239	$38,903,419	$65,989,658
5	3,148	2,432	4,420	4,372	3,469	$22,735,115	$38,105,912	$60,841,027
6	2,499	2,402	5,100	3,657	2,875	$19,015,454	$35,845,744	$54,861,198
7	1,983	2,307	5,710	3,049	2,379	$15,855,156	$32,795,733	$48,650,890
8	1,574	2,172	6,254	2,535	1,964	$13,184,091	$29,404,291	$42,588,383
9	1,249	2,014	6,737	2,103	1,619	$10,936,597	$25,961,665	$36,898,261
10	991	1,845	7,164	1,741	1,333	$9,052,796	$22,647,826	$31,700,622
			Per patient	5.472	4.448	$28,453	$31,289	$59,742

B. Data Markov Analysis: OldPB

Markov State				*Outcome*		*Cost*		
Cycle	*Nondialysis*	*Dialysis*	*Dead*	*Life Years*	*QALYs*	*Drug Cost*	*Dialysis Cost*	*Total Cost (Drug + Dialysis Costs)*
0	10,000	0	0	10,000	8,500	$20,000,000	$0	$20,000,000
1	7,259	1,741	1,000	8,571	7,070	$17,142,857	$33,154,578	$50,297,435
2	5,270	2,743	1,987	7,268	5,854	$14,535,999	$49,761,499	$64,297,498
3	3,826	3,249	2,925	6,111	4,830	$12,222,468	$56,130,756	$68,353,224
4	2,777	3,427	3,795	5,105	3,972	$10,209,112	$56,395,764	$66,604,875
5	2,016	3,397	4,587	4,241	3,259	$8,482,116	$53,228,764	$61,710,880
6	1,464	3,238	5,298	3,508	2,668	$7,016,915	$48,327,115	$55,344,029
7	1,062	3,007	5,930	2,892	2,181	$5,784,369	$42,742,767	$48,527,136
8	771	2,741	6,488	2,377	1,779	$4,754,494	$37,104,611	$41,859,105
9	560	2,464	6,976	1,949	1,450	$3,898,592	$31,767,790	$35,666,381
10	406	2,192	7,402	1,595	1,181	$3,190,375	$26,913,352	$30,103,727
			Per patient	5.362	4.274	$10,724	$43,553	$54,276

the NewPB and OldPB group. It was assumed that patients continued to receive medication (either NewPB or OldPB) until death. Costs were obtained from a retrospective review of Medicare data, and adjusted to 2013 costs. The quality-of-life estimates were derived from a study reporting utility values for CKD patients with and without dialysis (Exhibit 10.10). Both

EXHIBIT 10.12

Base Case Costs, Effects and Cost-Effectiveness of NewPB Cell versus OldPB for CKD with Hyperphosphatemia Over 10 Years

	Costs ($)	*Total Life Years*	*QALYs*	*Incremental Cost per Life Year Gained (ICER)*	*Incremental Cost per QALY Gained (ICER)*
NewPB	59,742	5.472	4.448	$49,759	$31,579
OldPB	54,276	5.363	4.274		

costs and outcomes were discounted at 5% per year. Patient outcomes were modeled for 10 years, and incremental cost-effectiveness ratios (ICERs) per life year gained and per QALY gained were calculated for NewPB relative to OldPB (see Exhibit 10.11 for model and calculations).

RESULTS: Exhibit 10.12 shows that the total costs and effects, in terms of life years and QALYs for patients treated with NewPB over 10 years and applying for a discount rate of 5%, were $59,742, 5.472 LYs, and 4.448 QALYs, respectively. For those patients treated with OldPB, the costs, life years and QALYs were $54,276, 5.363 LYs, and 4.274 QALYs,. respectively. With these estimates, the ICER of NewPB compared with OldPB was $49,759 per life year gained and $31,579 per QALY gained. The results of probabilistic sensitivity analyses are shown in Exhibit 10.13 and 10.14. Exhibit 10.13 presents the scatter-plot diagrams with a maximum willingness-to-pay (WTP) of $50,000/QALY, which is the joint distribution of the mean incremental costs and mean incremental effects. All of the estimates fell in quadrants I and II of the cost-effectiveness plane (although the vast majority fell in quadrant I). These results suggest that when varying costs and utility values within reasonable ranges, NewPB was either more costly and more effective, or in a few cases, less costly and more effective than OldPB. The mean values for each group were used to generate acceptability curves over a range of WTP values (Exhibit 10.14).

EXHIBIT 10.13

Cost-Effectiveness Plane of NewPB versus OldPB for CKD Patients with Hyperphosphatemia with a Maximum Willingness-to-Pay Level of $50,000 per QALYs

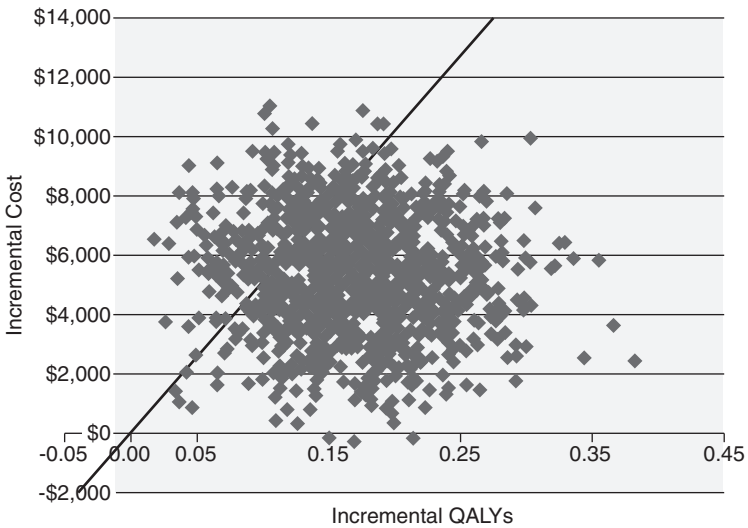
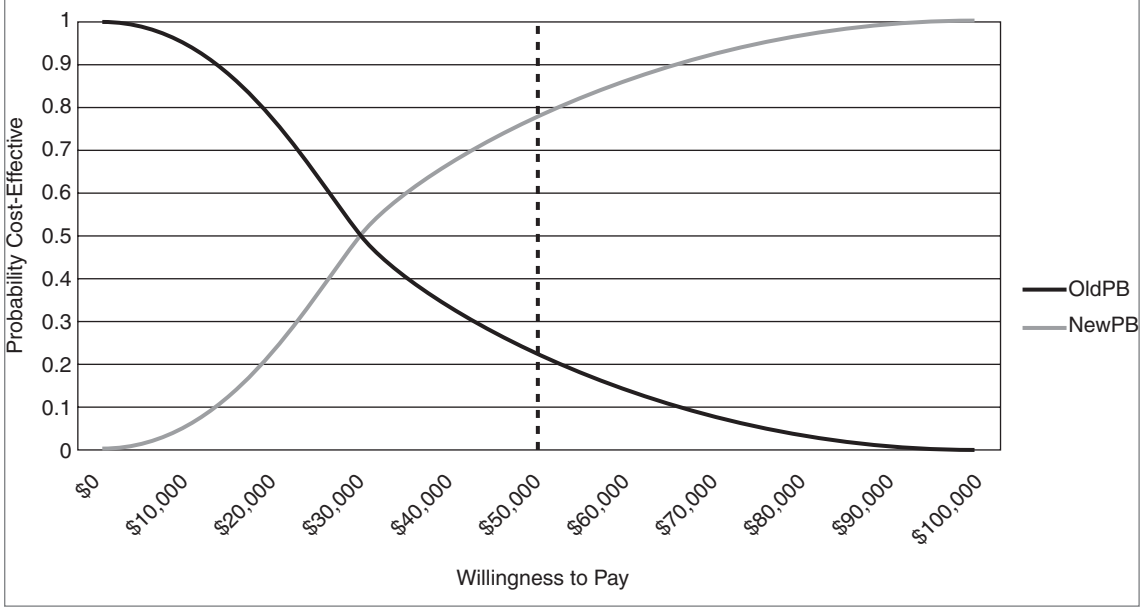


EXHIBIT 10.14

Cost-Effectiveness Acceptability Curves of NewPB versus OldPB for CKD Patients with Hyperphosphatemia



The cost-effectiveness acceptability curve illustrates a 79.5% probability of NewPB being cost-effective at the $50,000 WTP threshold.

DISCUSSION AND CONCLUSIONS: Limitations of this study include the assumption of efficacy data. The efficacy data from the randomized clinical trial was based on a relatively short duration of follow-up. Estimated outcomes for 10 years were modeled based on this short-term data. Hospitalization and cardiovascular event data were not collected in the randomized clinical trial. Overall, this analysis indicates that the long-term benefits of NewPB versus OldPB in terms of overall survival and inception of dialysis in patients with CKD and hyperphosphatemia from the perspective of the US payer. The results of this analysis demonstrate that NewPB represents a cost-effective alternative to OldPB for the treatment of hyperphosphatemia in patients with CKD in the US.

WORKSHEET FOR CRITIQUE OF MARKOV ANALYSIS COMPOSITE ARTICLE 2

1. Complete Title?

2. Clear Objective?

3. Appropriate Alternatives?

4. Alternatives Described?

5. Perspective Stated?

6. Type of Study?

7. Relevant Costs?

8. Relevant Outcomes?

9. Adjustment or Discounting?

10. Reasonable Assumptions?

11. Sensitivity Analyses?

12. Limitations Addressed?

13. Generalizations Appropriate?

14. Unbiased Conclusions?

ANSWERS

1. **Complete Title:** The title does include the type of study (cost-effectiveness) and the population (CKD patients). Although it lists one alternative (NewPB) it does not list the other alternative (OldPB).
2. **Clear Objective:** The objective was clearly stated as " ... to assess the cost-effectiveness of NewPB compared with OldPB in patients with CKD."
3. **Appropriate Alternatives:** Both medications are fictional—authors provide some comparisons of OldPB and NewPB.
4. **Alternatives Described:** No dosing given—may have to go to randomized controlled trial publication to determine dosing.
5. **Perspective Stated:** The perspective was clearly stated as the US payer perspective. Thus, only direct medical costs were included.
6. **Type of Study:** The study has been identified as a cost-effectiveness analysis. The outcomes were measured as both life years (LYs) gained—a CEA—and QALYs gained—a CUA. However the CUA is a type of CEA, so the title just including the term CEA is appropriate.

7. **Relevant Costs:** Based on the stated perspective, the direct medical costs of medication and dialysis treatment were included. Costs of treating side effects of medications should have been addressed.
8. **Relevant Outcomes:** LYs and QALYs are important outcomes in the treatment of CKD patients since both length and quality of life are affected by the disease and treatment.
9. **Adjustment and Discounting:** All costs were adjusted to 2013 US dollars and discounting for the future 10 years was conducted at a rate of 5%.
10. **Reasonable Assumptions:** It was assumed that the QALYs values were valid and the probabilities and costs obtained from literature were accurate. It was assumed that results from short term trials would extrapolate to 10 years. It was assumed that the cost-effectiveness threshold would be below $50,000.
11. **Sensitivity Analyses:** Sensitivity analyses were conducted by varying the costs and utility values using a technique called probability sensitivity analysis—results are illustrated in the scatterplot. The discount rate could also have been varied.
12. **Limitations Addressed:** Limitations on using short term efficacy data are addressed. Other outcomes cost (e.g., costs of side effects of medications), and effect of different rates of discounting were not addressed.
13. **Generalizations Appropriate:** The analysis included input costs and probabilities. A researcher could re-run the analysis with data specific for a different population. The authors did not address generalization—the appropriateness depends on the generalizability of the trial population used for data estimates.
14. **Unbiased Conclusions:** The authors do not overstate their results. Based on these numbers and sensitivity analyses, NewPB is, on average, more expensive that than OldPB, but provides better outcomes (LYs and QALYs) at a reasonable cost.

QUESTIONS/EXERCISES

An online coaching program has been developed for patients with borderline hypertension. A total of 100 patients are randomized to receive the coaching, and 100 patients serve as control subjects. It has been shown that for the first year after beginning the program, 90% with coaching were not considered hypertensive (normal or borderline blood pressure) and 10% were prescribed medication to control their blood pressure. In the control group (no coaching), 80% were not considered hypertensive after 1 year and 20% were prescribed blood pressure medication. Patients in the coaching group continue to receive coaching even if they are prescribed medication. The cost per year per patient for the coaching program is $50. The cost per year per patient for medication is $500. Assuming that these probabilities are constant for the next 4 years and that after patients begin medication, they must continue it for the rest of the study (absorbing state), answer the following questions. (Some cells have been filled in to help you get started.)

FOR 100 PATIENTS IN THE COACHING PROGRAM:

Prevention Coaching Program	*Subjects without Hypertension (n)*	*Subjects with Hypertension (n)*	*Cost of Coaching Program*	*Cost of Medication*	*Total Costs*
Cycle 1	100	0	$5,000	$0	$5,000
Cycle 2	90	10	$5,000	$5,000	$10,000
Cycle 3	81	19	$5,000	$9,500	$14,500
Cycle 4					
Cycle 5					
Total					

FOR 100 PATIENTS WITHOUT THE COACHING PROGRAM:

Prevention Coaching Program	*Subjects without Hypertension (n)*	*Subjects with Hypertension (n)*	*Cost of Coaching Program*	*Cost of Medication*	*Total Costs*
Cycle 1	100	0	$0	$0	$0
Cycle 2	80	20	$0	$10,000	$10,000
Cycle 3	64	36	$0	$18,000	$18,000
Cycle 4					
Cycle 5					
Total					

1. What are the total costs for the patients in the coaching group if no discounting is conducted? If a 5% discount rate (beginning cycle 2) is used?

2. What are the total costs for the patients in the control group (no coaching) if no discounting is conducted? If a 5% discount rate (beginning cycle 2) is used?

3. If the online counseling costs are considered input costs and benefits are calculated as cost savings due to less medication costs, what is the benefit-to-cost ratio of the program with and without discounting?

4. Would using a half-cycle correction be appropriate in this example? Why or why not?

5. What other costs and outcomes would be included in a more clinically relevant (and more complex) model?

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SUGGESTED READINGS

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