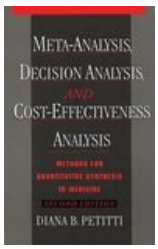

Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis (2nd edn)

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https://doi.org/10.1093/acprof:oso/9780195133646.001.0001

Published: 11 November 1999 **Online ISBN:** 9780199863761 **Print ISBN:** 9780195133646

CHAPTER

9 Complex Decision Problems

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https://doi.org/10.1093/acprof:oso/9780195133646.003.09

Published: November 1999

Abstract

This chapter describes how to build and analyze decision trees with more than two alternative interventions, more that two outcomes, or both. Life expectancy is often the outcome measure in decision analysis. Its estimation is also integral to many cost-effectiveness analyses. The chapter discusses the estimation of life-expectancy using the declining exponential approximation of life expectancy (DEALE). It introduces Markov models as a way to represent complex, time-related processes in a decision analysis. The difference between a Markov model and a Markov chain is explained.

Keywords: decision analysis, life-expectancy, DEALE, cost-effectiveness analysis, Markov model, Markov chain

Subject: Public Health, Epidemiology

Collection: Oxford Scholarship Online

Chapter 2 presented a simple decision analysis. The decision analysis was simple because only two alternative interventions were compared, because the events between the intervention and outcome required estimation of only a few probabilities, and because the outcome measure was a simple dichotomous measure—life or death. Decision analysis for most medical problems is more complex because it often involves comparison of more than one treatment or intervention, because the outcomes of interest are not always simple dichotomies, and because the chain from treatment to outcome involves many events, requiring the estimation of many probabilities. This chapter begins the description of decision analysis for more complex situations by showing how to build and analyze decision trees with more complex outcomes and more complex intervening events. Chapter 10 describes the approach to estimating probabilities in a decision analysis. Measuring utilities—the value of various outcomes to patients and society—in order to conduct a utility analysis is considered in Chapter 11. Chapter 13 discusses the incorporation of measures of utility into decision analysis and cost-effectiveness analysis. Sensitivity analysis is covered in Chapter 15.

Section 9.1 describes decision analysis involving comparison of more than two alternative treatments or interventions. Section 9.2 describes decision analysis with more than two outcomes. Section 9.3 describes

decision analysis involving many intervening events between intervention and outcome. Section 9.4 shows how to estimate life expectancy, which is commonly used as a measure of outcome in decision analysis, using the declining exponential approximation of life expectancy (DEALE). Section 9.5 discusses the use of Markov models to represent complex, time-related processes in a decision analysis.

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9.1 MORE THAN TWO ALTERNATIVE TREATMENTS OR INTERVENTIONS

More than two alternative treatments for a condition may be available, or there may be more than one strategy for addressing a problem. In this case, the decision node of the decision tree has more than two arms. The expected outcome for each arm is calculated by the process of folding back and averaging, and the strategies are compared in relation to one another.

EXAMPLE: Revaccinating children is one strategy for addressing the problem of a measles epidemic. An alternative public health strategy to cope with the epidemic would be a strategy of excluding all children with any rash or fever from school for a two-week period. This "quarantine" strategy would be expected to decrease the likelihood of exposure to measles for children who remain at school and would prevent measles and its consequences for this reason.

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Figure 9-1 is a decision tree depicting these three alternative courses of ↳ action—revaccination, quarantine, and no revaccination (do nothing). The decision tree has been simplified by removing the branches which have probabilities of 1.0 or 0, a process called "pruning."

Based on review of the literature, it is estimated that quarantine will decrease the likelihood of exposure to measles from 0.20 to 0.15. Table 9-1 shows the three alternatives with the relevant probabilities recorded. A new subtable has been added to represent the new decision alternative—quarantine—and the relevant probabilities are recorded in the table.

The estimates of the expected number of deaths from measles for the revaccination and no-revaccination (do-nothing) strategies do not change. The expected number of deaths from measles for the decision alternative, quarantine, is estimated by the process of folding back and averaging. The products of the probabilities in each row of the subtable are calculated. Then, the expected number of deaths from measles is estimated by adding the entries in the columns corresponding to the rows labeled "die." The expected number of deaths is

0.000114 + 0.000000 + 0.000000 + 0.000000 = 0.000114

The comparison of me revaccination and no-revaccination strategies does not change. Revaccination is estimated to prevent 12.9 deaths per 100,000 children compared with no revaccination. The strategy of quarantine is compared with the strategy of no-revaccination (do nothing) by subtracting the expected numbers of deaths from measles as follows:

0.0000152 - 0.000114 = 0.000038

Interpreting these figures from the decision standpoint, the analysis shows that, while quarantine is expected to prevent 3.8 deaths per 100,000 compared with doing nothing, revaccination prevents 12.9 deaths per 100,000. Compared with doing nothing, the strategy of revaccination is superior to the strategy of quarantine.

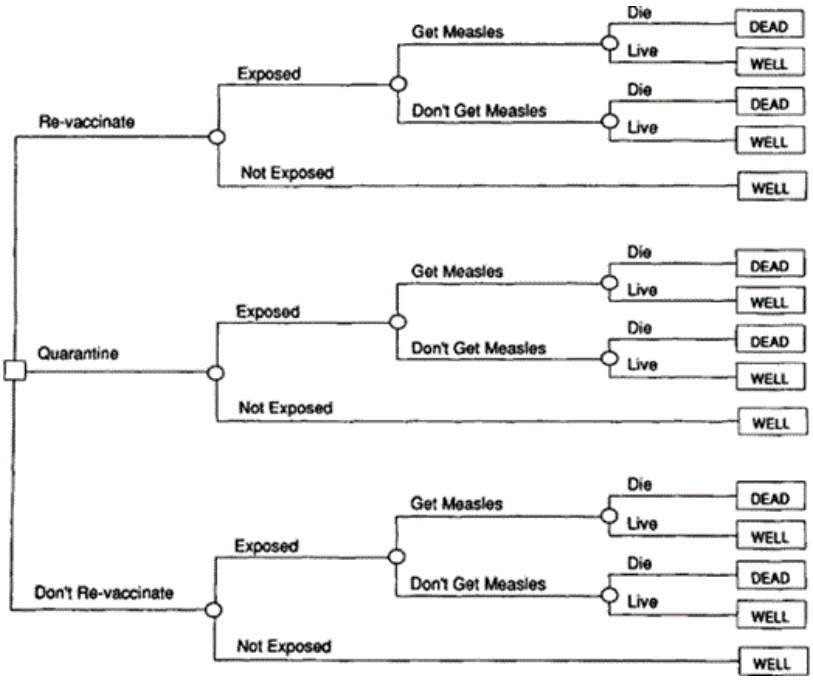

Figure 9-1 Decision tree comparing three strategies for dealing with the measles epidemic: revaccination, quarantine of infectious cases, and no revaccination.

Table 9-1 Calculations to show results of decision analysis comparing three options: revaccination, quarantine, and no revaccination

Product	Revaccination			
	Probability of Exposure	Probability of Getting Measles	Probability of Outcome	
0.000023	0.2	0.05	0.0023	die
0.009977	0.2	0.05	0.9977	don't die
0.000000	0.2	0.95	0.0000	die
0.190000	0.2	0.95	1.0000	don't die
0.000000	0.8	0	0.0023	die
0.000000	0.8	0	0.9977	don't die
0.000000	0.8	1	0.0000	die
0.800000	0.8	1	1.0000	don't die
Sum for deaths 0.000023				

Product	No Revaccination			
	Probability of Exposure	Probability of Getting Measles	Probability of Outcome	
0.000152	0.2	0.33	0.0023	die
0.065848	0.2	0.33	0.9977	don't die
0.000000	0.2	0.67	0.0000	die
0.134000	0.2	0.67	1.0000	don't die
0.000000	0.8	0	0.0023	die
0.000000	0.8	0	0.9977	don't die
0.000000	0.8	1	0.0000	die
0.800000	0.8	1	1.0000	don't die
Sum for deaths 0.000152				

Product	Quarantine			
	Probability of Exposure	Probability of Getting Measles	Probability of Outcome	
0.000114	0.15	0.33	0.0023	die

0.049386	0.15	0.33	0.9977	don't die
0.000000	0.15	0.67	0.0000	die
0.100500	0.15	0.67	1.0000	don't die
0.000000	0.85	0	0.0023	die
0.000000	0.85	0	0.9977	don't die
0.000000	0.85	1	0.0000	die
0.850000	0.85	1	1.0000	don't die
Sum for deaths 0.000114 Differences Revaccination compared with no revaccination 0.000129 12.9 deaths per 100,000 Quarantine compared with no revaccination 0.000038 3.8 deaths per 100,000				

This was a hypothetical example. In real-life applications, it is also common to compare more than one intervention in a decision analysis.

> *EXAMPLE:* Figure 9-2 shows the graphical representation of the decision options in the decision analysis of warfarin and aspirin for patients with nonvalvular atrial fibrillation that was discussed in Chapter 2. This is an example of a real analysis examining more than two alternative interventions. In this example warfarin, aspirin, and no therapy are examined as alternatives for the management of patients with nonvalvular atrial fibrillation.

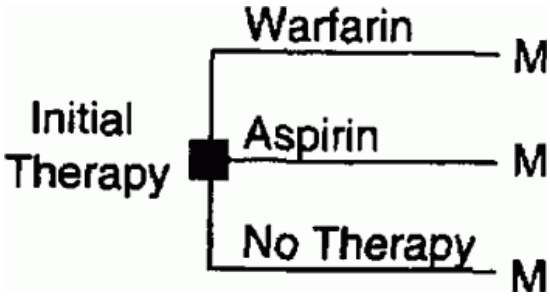

Figure 9-2 Decision tree depicting the choice among three treatment options for patients with nonvalvular atrial fibrillation. (Reproduced with permission from Gage et al., *Journal of the American Medical Association*, 1995; 274:1840.)

9.2 MORE THAN ONE OUTCOME

The outcomes of most medical treatments are not simple dichotomies. Many medical treatments have side
p. 143 effects that need to be taken into account in making ↳

p. 144 ↳
decisions about their net benefit and whether or not to recommend them. In addition, the beneficial and adverse consequences of many medical treatments and interventions include outcomes other than life and death.

In the simplest case, there are several mutually exclusive outcomes of an intervention. In this case, the decision tree is modified by including multiple boxes at the terminal or outcome node. This situation is shown for a hypothetical case in Figure 9-3 . The probabilities of each outcome are estimated by literature review and recorded on the decision tree and analyzed by the process of folding back and averaging. In this situation, the decision analysis yields separate estimates of the value of each outcome in comparison with each alternative intervention.

EXAMPLE: Measles can cause blindness as well as death. Figure 9-4 shows the decision tree based
p. 145 on the example used in Chapter 1 as modified to ↳ include the occurrence of blindness as an outcome. Blindness and death are mutually exclusive outcomes, and it is proper to record them at the terminal node of the decision tree.

Based on review of the literature, it is determined that the likelihood of blindness following measles is 45 cases per 100,000 cases of measles. The likelihood of blindness in the absence of measles is assumed to be 0.0.

Table 9-2 shows the numbers used to analyze the decision tree, again illustrating the analysis as a spreadsheet to simplify understanding of the calculations that are done to analyze the tree. In analyzing the decision tree, for each row, the product of the probability values in each column is computed. The expected number of deaths for the revaccination arm is estimated by summing the entries in the product column for the rows labeled with death in the upper part of the table. The expected number of cases of blindness in the revaccination arm is estimated by summing the entries in the product column for the rows labeled blindness in the upper part of the table. Thus, the expected number of deaths is just as it was in Chapter 2:

p. 146 ↳ 0.000023 + 0.000000 + 0.000000 + 0.000000 = 0.000023

The expected number of cases of blindness is

0.00045 + 0.000000 + 0.000000 + 0.000000 = 0.000045

p. 147

The expected number of cases of blindness and of death in the no-revaccination arm is estimated by summing the entries in the product columns ↳ for the rows corresponding to the relevant outcome entry. The expected number of cases of blindness is

0.000297 + 0.000000 + 0.000000 + 0.000000 = 0.000297

The expected number of deaths for the no-revaccination strategy is

0.000152 + 0.000000 + 0.000000 + 0.000000 = 0.000152

The strategies of revaccination and no-revaccination are compared for these two outcomes by subtracting the expected number of deaths and the expected number of cases of blindness. The expected number of deaths from measles is

0.000152 - 0.00023 = 0.000129

which is the same as in the prior example. The expected number of cases of blindness comparing revaccination with no-revaccination is

0.000297 - 0.000045 = 0.000252

Translated to numbers per 100,000 persons revaccinated, the revaccination strategy prevents 12.9 deaths from measles and 25.2 cases of blindness.

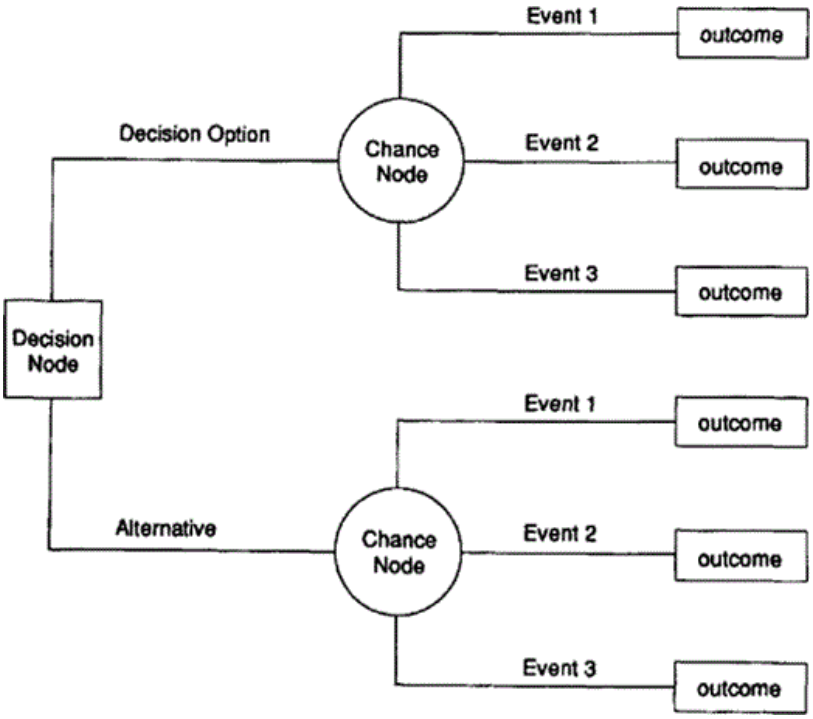

Figure 9-3 Hypothetical decision tree where there is more than one outcome.

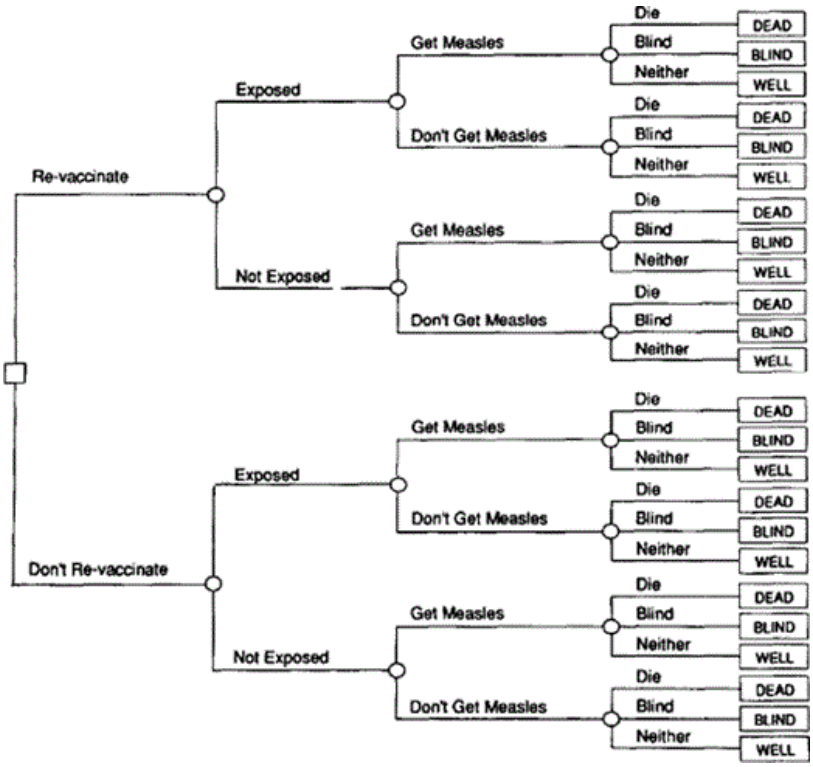

Figure 9-4 Decision tree for the measles problem where the outcomes of interest in the analysis are death, blindness, and remaining well.

Table 9-2 Calculations to show results of decision analysis for revaccination versus no revaccination where measles has three outcomes: death, blindness, well

Product	Revaccination			
	Probability of Exposure	Probability of Getting Measles	Probability of Outcome	
0.000023	0.2	0.05	0.0023	die
0.000045	0.2	0.05	0.0045	blind
0.009932	0.2	0.05	0.9932	well
0.000000	0.2	0.95	0.0000	die
0.000000	0.2	0.95	0.0000	blind
0.190000	0.2	0.95	1.0000	well
0.000000	0.8	0	0.0023	die
0.000000	0.8	0	0.0045	blind
0.000000	0.8	0	0.9932	well
0.000000	0.8	1	0.0000	die
0.000000	0.8	1	0.0000	blind
0.800000	0.8	1	1.0000	well
Sum for deaths 0.000023	Sum for blind 0.000045			

Product	No Revaccination			
	Probability of Exposure	Probability of Getting Measles	Probability of Outcome	
0.000152	0.2	0.33	0.0023	die
0.000297	0.2	0.33	0.0045	blind
0.065551	0.2	0.33	0.9932	well
0.000000	0.2	0.67	0.0000	die
0.000000	0.2	0.67	0.0000	blind
0.134000	0.2	0.67	1.0000	well
0.000000	0.8	0	0.0023	die
0.000000	0.8	0	0.0045	blind
0.000000	0.8	0	0.9932	well
0.000000	0.8	1	0.0000	die
0.000000	0.8	1	0.0000	blind

0.800000	0.8	1	1.0000	well
Sum for deaths 0.000152	Sum for blind 0.000297			
Differences between revaccination and no revaccination Death 0.000129 Blind 0.000252				

In practice, the number of outcomes of a particular intervention can be large. Outcomes may be gradations of severity of a single outcome, reflecting the reality of the manifestation of illness in individuals.

> *EXAMPLE:* In the decision model used to compare warfarin and aspirin with no treatment for patients with nonvalvular atrial fibrillation that was discussed in Chapter 2, Gage et al. identified 10 relevant outcomes. These are illustrated in Figure 9-5. They include life and death as well as varying grades of the severity of stroke. Stroke caused by intracranial hemorrhage is distinguished from ischemic stroke as an outcome because the consequences of the two types of stroke are different.

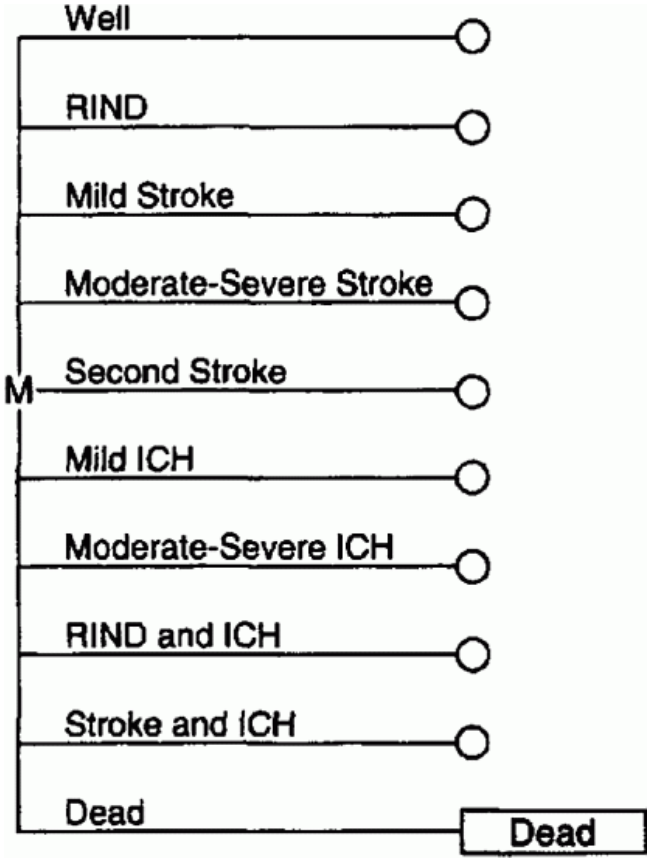

Figure 9-5 Decision tree showing health state outcomes for warfarin and aspirin therapy. RIND refers to reversible ischemic neurologic deficit. ICH refers to intracranial hemorrhage. Modified from Gage et al. (1995). (Reproduced with permission from Gage et al., *Journal of the American Medical Association*, 1995; 274:1840.)

9.3 MANY INTERVENING EVENTS

For most medical problems, the description of the pathway between a decision and its outcome involves many more intervening events than in the example that has been used in this book so far. The decision trees that result from the proper description of medical problems can be very complex. There are often many intervening events that themselves are determined by complex events.

> *EXAMPLE:* Jordan et al. (1991) did a decision analysis to inform clinical decisions about whether or not to give isoniazid prophylaxis routinely to HIV seropositive users of intravenous drugs. Figure 9-6 is the decision tree for this analysis. When the isoniazid arm of the tree is followed along its uppermost branches, the tree includes the occurrence or nonoccurrence of isoniazid toxicity. If
> p. 148 isoniazid toxicity occurs, it is either fatal or nonfatal. If ↳
>
> p. 149 ↳
> toxicity is nonfatal, then infection with tuberculosis either occurs or does not occur. If infection occurs, active tuberculosis may or may not result. If active tuberculosis occurs, it may be either fatal or nonfatal. The other branches of the tree can be similarly described.

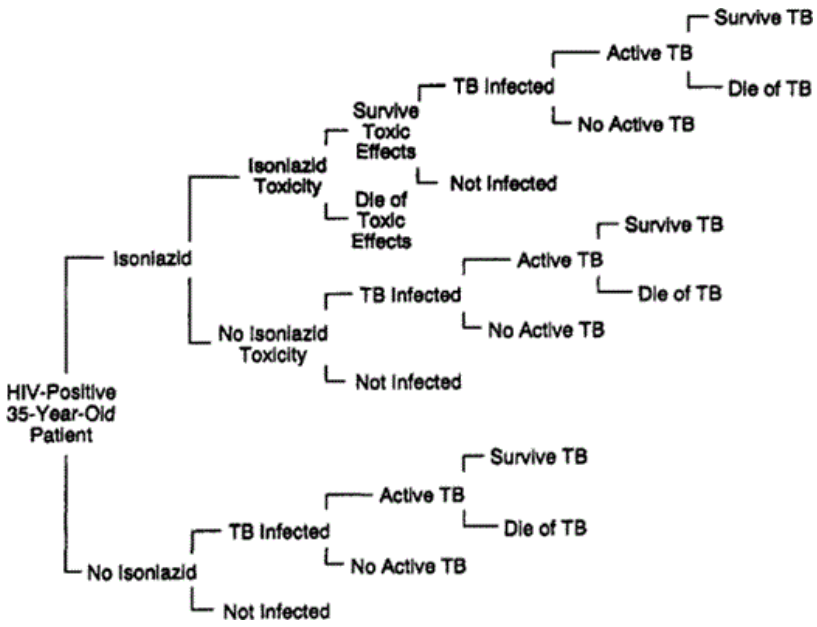

Figure 9-6 Decision tree used for analysis of prophylactic isoniazid versus no treatment in HIV-infected intravenous drug users. (Reproduced with permission from Jordan et al., *Journal of the American Medical Association*, 1991;265:2988.)

Developing a decision tree that properly represents the problem that is posed is one of the most important challenges of decision analysis. The construction of complex decision trees is described in introductory textbooks by Weinstein and Fineberg (1980) and Sox, Blatt, and Higgins (1988), and these descriptions will not be repeated in this book. A software package that helps to construct complex decision trees, Decision Maker, has been developed and can be useful.

The methods for analyzing complex decision trees are a logical extension of the methods that were described in Chapter 2 and in Sections 9.1 and 9.2 and involve the process of folding back and averaging. The introductory textbooks by Weinstein and Fineberg (1980) and Sox et al. (1989) give examples of the analysis of complex decision trees, and such examples will not be provided in this book. For complex decision trees, the challenge

of analysis is keeping track of the calculations. Specialized computer software is useful for this purpose. Otherwise, the help of a computer programmer may be necessary.

9.4 ESTIMATING LIFE EXPECTANCY

9.4.1 Overview

The outcome of interest in a decision analysis is often life expectancy and not just life or death. Since everyone must ultimately die, it is obvious that life expectancy is the most appropriate measure of the effect of an intervention whose most important effect is on survival.

Life expectancy is defined by actuaries as the average future lifetime of a person, and it is usually estimated for persons of a specific age, sex, and race. Actuarial methods to estimate life expectancy are based on specialized statistical life-table functions that rely on data on mortality rates specific for age, sex, and race. The age-, sex-, and race-specific mortality rates are based on death certificate data and census data.

Published tables of vital statistics describe the life expectancies of healthy persons. These published life expectancies are often all that is needed in a decision analysis, because the central task of the decision analysis is to estimate the effect of illness, with or without an intervention, on life expectancy.

In very rare cases, life expectancy in persons with an illness who have and have not undergone the intervention and its alternatives has been compared directly in a randomized trial or in a follow-up study. In these rare cases, the information on life expectancy can be used in a decision analysis without modification.

More often, available information on life expectancy in persons with a disease is in the form of overall mortality rates, five-year survival rates, or median survival. In general, the effect of interventions on life
p. 150 expectancy is measured as the relative ↳ risk or the odds of mortality in a given interval in those who have the intervention compared with those who do not.

These kinds of information are not easily translated into information about life expectancy. For example, an intervention that halves the relative risk of death in a five-year follow-up interval does not double life expectancy. The effect on life expectancy of a disease that increases five-year survival by 20% is dependent on the age, sex, and race of the person, since life expectancy in the absence of the intervention is also dependent on these factors.

The estimation of life expectancy from information on overall mortality, five-year survival, median survival, and the relative risk of death in a given interval can be done with actuarial methods using information on age-, sex-, and rate-specific mortality. These actuarial methods require complex calculations that will not be described. A method for estimating life expectancy described by Beck, Kassirer, and Pauker (1982) and Beck et al. (1982) that requires only information on the age-, sex-, and race-specific life expectancy from a table of vital statistics and an estimate of the effect of the disease, treatment, or intervention on mortality has been widely used in decision analysis. The method, called the declining exponential approximation of life expectancy (DEALE), is simple to use, and it has been shown to closely approximate estimates of life expectancy based on actuarial methods (Beck, Kassirer, Pauker 1982).

9.4.2 Using the DEALE to Estimate Life Expectancy

Use of the DEALE assumes that survival follows a declining exponential curve. If this assumption is true, then life expectancy for a person of a given age, sex, and race can be estimated as the reciprocal of the mortality rate:

$$\text{life expectancy} = \frac{1}{\text{mortality}}$$

For a person of a specific age, sex, and race, this relationship can be used to estimate mortality from published life tables:

$$m_{asr} = \frac{1}{le_{asr}}$$

where m_{asr} is the average mortality rate of a person of a given age, sex, and race and le_{asr} is the life expectancy of a person of a given age, sex, and race as described in published life tables.

If an intervention decreases mortality by an amount m, then life expectancy for the person who has the intervention l_{ei} is estimated as

$$le_i = \frac{1}{m_{asr} - m}$$

> *EXAMPLE:* Imagine that an intervention decreases the probability of death by 0.001 per year. The problem is to determine the effect of the intervention on life expectancy in a 45-year-old woman.

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1. Determine the average life expectancy at age 45 from a table of vital statistics:
   le_{asr} = 37.8 years

2. Estimate the average mortality rate where

$$m_{asr} = \frac{1}{le_{asr}}$$

$$m_{asr} = \frac{1}{37.8} = 0.026 \text{ per year}$$

3. Estimate the mortality rate in those who have the intervention by subtracting the mortality rate caused by the intervention from the average mortality rate:
   $m_i = m_{asr} - m$
   m_i = 0.026 - 0.001 = 0.025 per year

4. Estimate life expectancy in those who have the intervention where

$$le_i = \frac{1}{m_i}$$

$$le_i = \frac{1}{0.025} = 40.0 \text{ years}$$

5. Estimate the gain in life expectancy in those with the intervention compared with those without the intervention by subtraction:
   gain in life expectancy = 40.0 − 37.8 = 2.2 years

When the goal of the analysis is to estimate the effect of a disease on life expectancy, the same method can be used. In this case, excess mortality from the disease, m_e is added to the mortality rate specific for age, sex, and race. That is, in step 3 described above:

$$m_d = m_{asr} + m \quad \text{and} \quad le_d = \frac{1}{m_d}$$

> *EXAMPLE:* The effect of coronary heart disease on life expectancy in 45-year-old white women needs to be estimated. The excess mortality from coronary heart disease is 0.015 per year. The life expectancy of 45-year-old women with coronary heart disease is
>
> $$m_d = m_{asr} + m = 0.026 + 0.015 = 0.041$$
> $$le_d = \frac{1}{m_d} = \frac{1}{0.041} = 24.4 \text{ years}$$
>
> Coronary heart disease reduces estimated life expectancy by 13.4 years (37.8 years − 24.4 years).

p. 152 Excess mortality from various diseases and the effects of interventions on mortality per year are sometimes measured directly, and these equations are then directly applicable. More often, available information consists of overall mortality rate, five-year survival, or median survival in persons with the disease or having the intervention. Only a curve describing the survival of persons with the disease or having the intervention may be available. These measures of observed mortality are compound measures of mortality. All are composed of baseline mortality—the mortality expected in the general population plus either the excess mortality due to the disease or lower mortality due to the intervention. Before applying the DEALE, measures of compound mortality must be decomposed into baseline and excess mortality or baseline and saved mortality. Methods to decompose different kinds of compound measures of mortality so that they can be used to estimate life expectancy using the DEALE are described in detail by Beck et al. (1982), and they will not be described here.

9.5 MARKOV MODELS

9.5.1 Overall Goal

A Markov model is used in decision analysis to try to more accurately represent complex processes that involve transitions in and out of various states of health and risks that change over time (Beck and Pauker 1983; Sonnenberg and Beck 1993). Complex transitions and events that occur more than once or with uncertain timing are difficult to handle with simple decision trees. Markov models are used to attempt to capture the complexity of these transitions and incorporate it into the decision analysis.

> *EXAMPLE:* A decision analysis is being done to try to determine whether to recommend sclerotherapy for men with bleeding esophageal varices. Figure 9-7 is a decision tree drawn to represent this problem. The tree does not accurately represent the complexity of the problem of treating esophageal varices. Thus, a man with bleeding esophageal varices is initially ill and bleeding. He can either recover completely or die from the bleed. If he recovers, he is again at risk of bleeding from the varices. If another bleed from the varices occurs, he may recover or he may die from the bleed. Transitions in and out of states of health occur until the man dies of a bleed or from some other cause. The likelihood of death from other causes is high in men with bleeding esophageal varices. A decision analysis that tries to assess the effect of a treatment for bleeding esophageal varices on life expectancy should take into account the fact that transitions into and out of states of complete health occur and when they occur.

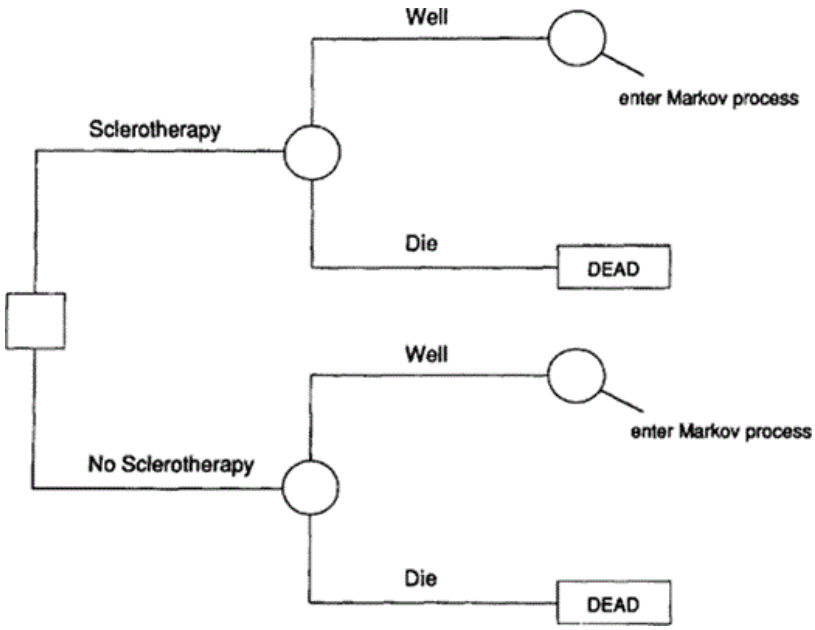

Figure 9-7 Decision tree for comparison of sclerotherapy versus no sclerotherapy for bleeding esophageal varices.

9.5.2 Application of the Method

9.5.2.1 *Overview*

There are four steps in a decision analysis that uses a Markov model to represent a process between the
p. 153 intervention and outcome. The first step is to determine the ↳ health states that will be modeled and to describe the ways in which transitions into and out of the health states will be allowed to occur in the model. The second step is to choose the length of the cycle that determines when transitions into and out of the various states that will be allowed. Third, the transition probabilities are estimated using the same methods that are used to estimate other probabilities in a decision analysis, as described in Chapter 10. Last, based on the estimates of the transition probabilities, the outcome with and without the intervention is determined by one of several methods.

9.5.2.2 *Choose States and Transitions*

It is common to represent the Markov process graphically. By convention, the states are defined as ovals or as circles. The time cycles are depicted on the left of the graph, and time runs downward on the graph. Arrows that link one state symbol with another state symbol are used to represent the allowed transitions between states in the model.

> *EXAMPLE:* Figure 9-8 is a graphic representation of the problem of bleeding esophageal varices that was described previously. In the figure, men are assumed to be bleeding from varices at time 0. In the interval from time 0 to time 1, all men with bleeding varices either become well or they die. In the
> p. 154 interval from time 1 to time 2, men who were well at time 1 can remain ↳ well, bleed again, or die from another cause. In the next interval, from time 2 to time 3, the men who bled again can recover (again) or die; the men who were well can remain well, rebleed, or die of another cause.

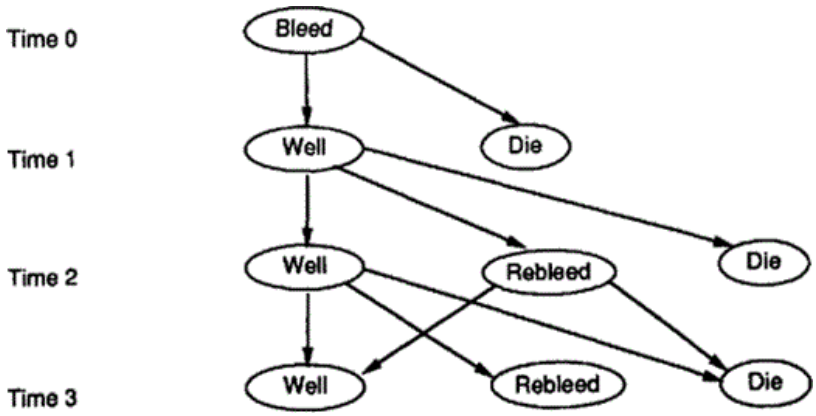

Figure 9-8 Graphical representation of Markov model of rebleeding after an initial episode of bleeding from esophageal varices.

9.5.2.3 *Choose Cycle Length*

The cycle length is the amount of time that elapses between successive evaluations of outcome. It is chosen to reflect the underlying biological process that is being modeled, and it may be short (weeks) or long (years). Computationally, longer cycles are less burdensome than shorter cycles, although the use of a computer program to carry out the Markov analysis makes consideration of the computational burden a relatively unimportant one.

EXAMPLE: The cycle length chosen for the problem of bleeding varices is one year. That is, the outcome in the hypothetical cohort will be evaluated at the end of one-year cycles.

9.5.2.4 *Determine Transition Probabilities*

The next step is to determine the transition probabilities. The literature is usually the source of information on transition probabilities. Most available information about transitions between clinical states is expressed in the form of a rate and not in the form of a probability. A rate is the number of events per unit time; it can vary from zero to infinity. A probability is a quantity that is unitless (time is built into it); it takes values from zero to one. A rate r can be used to estimate a transition probability p of an event occurring over a time interval t based on the following formula:

$$p = 1 - e^{-n}$$

where e is the base of the natural logarithm.

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EXAMPLE: In studies of men with bleeding esophageal varices, the rate of rebleeding is 51 per 100 per year. The transition probability from being well to rebleeding is

$$P_{rebleed} = 1 - e^{-0.51} = 1 - 0.60 = 0.40$$

This is the probability of a rebleed per year.

The probability of a rebleed per month is

$$P_{rebleed} = 1 - e^{-0.51 \div 12} = 1 - 0.96 = 0.04$$

Table 9-3 shows estimates of mortality at first bleed and subsequent bleeds, mortality from other causes, and the rate of rebleeding for men who do and do not undergo sclerotherapy as determined from a review of the literature. The transition probabilities per year calculated from these annual rates are also presented in the table.

Table 9-3 Rates per year and transition probabilities for sclerotherapy versus no sclerotherapy

Event	No Sclerotherapy		Sclerotherapy	
	Rate[a]	Transition Probability[b]	Rate[a]	Transition Probability[b]
Death at first bleed	0.91	0.60	0.69	0.50
Death of subsequent bleed	0.91	0.60	0.91	0.60
Rebleed	0.51	0.40	0.35	0.30
Death from other cause than bleed	0.51	0.40	0.51	0.40

a Per 100 per year.

b Per year.

9.5.2.5 *Estimate Outcome*

There are three main methods that can be used to provide information on life expectancy for the Markov process (Beck and Pauker 1983; Sonnenberg and Beck 1993): Monte Carlo simulation, analysis of hypothetical cohorts of persons (Markov cohort simulation), and matrix algebra. The method for determining life expectancy for a Markov process that is conceptually the easiest is the method in which outcomes in hypothetical cohorts of individuals with and without the intervention are determined iteratively, usually until all members of the hypothetical cohort have "died."

Monte Carlo simulation and the use of matrix algebra are somewhat more complex. The disadvantage of the matrix algebra approach is its restriction to problems with constant transition probabilities. An advantage of Monte Carlo simulation and matrix algebra solutions is that both provide estimates of the variability of the outcome measure. The interested reader is referred to the description by Beck and Pauker (1983) and Sonnenberg and Beck (1993).

p. 156 The following example uses the hypothetical cohort method (Markov cohort simulation).

> *EXAMPLE:* Table 9-3 gave the estimates of transition probabilities that are used in this example. Using these figures, in a hypothetical cohort of 100,000 men with bleeding esophageal varices at time T_0 who do not undergo sclerotherapy, it is estimated that 60,000 will die in the interval from T_0 to T_1 and 40,000 will be well. In the interval from T_1 to T_2 16,000 of those who are well at the start of the interval will rebleed, 16,000 will die of other causes, and 8000 will remain well. In the next interval, 9600 of those who bled in the prior interval will die of the rebleed and 6400 will become well; of those well at the end of the last interval, 3200 will rebleed, 3200 will die of other causes, and 1600 will remain well. Calculations are repeated for this hypothetical cohort until all members of the cohort are estimated to have died, as shown in Table 9-4.
>
> In a hypothetical cohort of 100,000 men who undergo sclerotherapy at the initial bleeding episode,
> p. 157 sclerotherapy is assumed to decrease the probability ↳ of death at the time of the first bleed from 0.60 to 0.50 and to decrease the probability of rebleeding in each subsequent interval from 0.4 to 0.3, but not to affect either the probability of death given a rebleed or the probability of death from other causes. In this hypothetical cohort, the numbers alive, bleeding, and well are as shown in Table 9-4.
>
> Once the numbers of men in states of being well, rebleeding, and death for each cycle have been calculated, the total number of years spent in the states of well or rebleed is determined by summing the relevant columns. This sum is divided by the size of the hypothetical cohort to determine the average cycle length spent in each of the two living states. Life expectancy is estimated as the sum of the average cycles spent in living states. In the no-sclerotherapy cohort, the average number of years in the well state is 0.62. In the state of bleeding, it is 1.25 years. Both the well state and the bleeding state are living states, and life expectancy is estimated as the sum of the average cycles in these two states, or 1.87 years. In the sclerotherapy cohort, life expectancy is estimated to be 2.12 years, the sum of the average number of years spent in the well state (0.86) and the average number spent in the state of bleeding (1.26). The estimated gain in life expectancy from sclerotherapy is estimated as the difference in these two life expectancies, which is 2.12 – 1.87, or 0.25 year.

Table 9-4 Markov process: calculations for hypothetical cohorts of men with bleeding esophageal varices who do or do not have sclerotherapy

Time	No Sclerotherapy			Sclerotherapy		
	Well	Bleed	Dead	Well	Bleed	Dead
0	0	100,000	0	0	100,000	0
1	40,000	0	60,000	50,000	0	50,000
2	8,000	16,000	16,000	15,000	15,000	20,000
3	8,000	3,200	12,800	10,500	4,500	15,000
4	2,880	3,200	5,120	4,950	3,150	6,900
5	1,856	1,152	3,072	2,745	1,485	3,870
6	833	742	1,433	1,417	824	1,989
7	464	333	778	755	425	1,061
8	225	186	386	396	227	557
9	119	90	202	210	119	294
10	59	48	102	111	63	155
11	30	24	53	59	33	82
12	16	12	26	30	18	44
13	9	6	13	16	9	23
14	4	3	8	9	4	11
15	0	0	7[a]	4	3	7
16	0	0	0	0	0	7[a]
Sum	62,495	124,996		86,202	125,860	
Average cycles[b]	0.62	1.25		0.86	1.26	
Life expectancy: no sclerotherapy		0.62 + 1.25 = 1.87 years				
Life expectancy: sclerotherapy		0.86 + 1.26 = 2.12 years				
Difference		2.12 − 1.87 = 0.25 year				

a The tail has been truncated.

b Sum/100,000.

9.5.3 Markov Chains Versus Markov Processes

Markov models can assume either that the probabilities of transition are constant over time or that they vary. The first class of models are Markov chain models; the second class are Markov process models. Modeling a problem as a Markov process is required whenever the death occurs remote in time to the intervention, or the cohort "ages." The preceding example used a Markov chain model. In the example, it was not necessary to take age into account because the underlying mortality rate from causes other than bleeding in a cohort of men with bleeding esophageal varices is so high that the increasing mortality rate with age does not come into play in the estimate of life expectancy. Methods for incorporating transition probabilities that vary over time into a decision analysis based on a Markov model are provided by Beck and Pauker (1983) and by Sonnenberg and Beck (1993).

9.5.4 Limitations

Use of a Markov model to represent a process assumes that the behavior of the process in any cycle depends only on that cycle (Sonnenberg and Beck 1993). That is, the transition from a given state is independent of the prior transitions. In the sclerotherapy example, this is equivalent to an assumption that the probability of death from bleeding is independent of the number of times that the person has bled in the past.

The transition state assumption is a fairly tenuous one in many medical applications. The problem can be
p. 158 overcome by creating separate states for subsets of ↳ the cohort with different prognoses. This increases the complexity of the analysis and the difficulty of estimating the probabilities.

Additional limitations on the use of Markov models arise because of the unavailability of information that would allow accurate estimation of transition probabilities. Special studies to estimate these are rarely undertaken, and data to derive the estimates may not be easily obtainable.