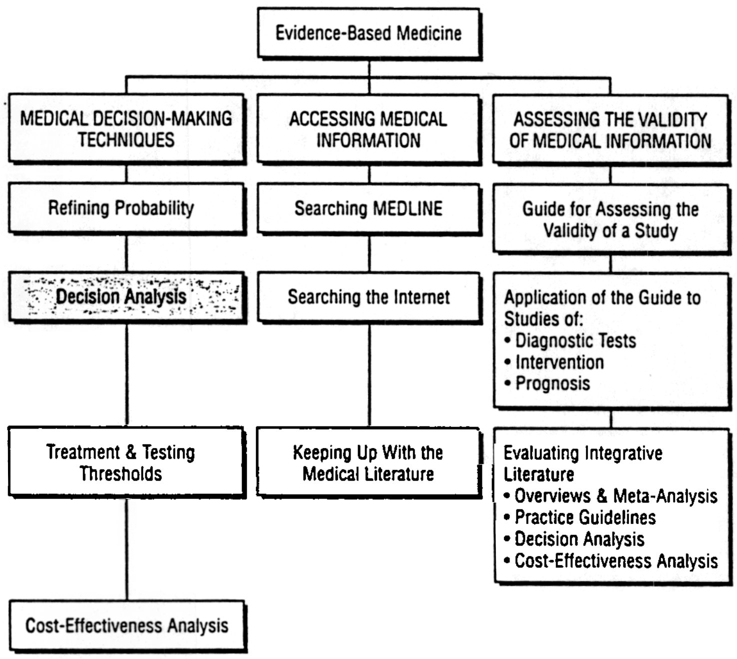
2

DECISION ANALYSIS

Michael G. Shlipak, MD, MPH

▸ OUTLINE



From: Friedland DJ et al: Evidence-Based Medicine: A Framework for Clinical Practice. Appleton & Lange, 1998.

You are discussing treatment options in your office with your patient, SM, a 40-year-old man who has persistent exacerbation of chronic ulcerative colitis. He continues to experience severe abdominal pain, poor appetite, and diarrhea despite taking high doses of oral corticosteroids. In his 20 years of living with ulcerative colitis, during which he has experienced frequent severe flares of the disease, SM has never seemed so distraught. "Doc, you've got to do something. You've got to make me better! I just can't take this any longer!" As his primary care physician for the past decade, you reflect on his long-term battle with ulcerative colitis—the hospitalizations, the occasional bouts of fecal incontinence, and the constant fear of colorectal cancer. You realize that SM is at a crossroads concerning his disease and that the two of you must make a decision.

Unfortunately, your consultants are in disagreement about a decision. The general surgeon recommends total colectomy, using a relatively new technique—**ileal pouch-anal anastomosis.** This two-stage procedure involves total colectomy, but the ileum is anastomosed to the anus so that ileostomy is usually avoided. Because a "pouch" is created from the ileum to serve as a rectum, continence is usually maintained; however, many patients experience daily soiling of stool that requires them to wear diapers. On the basis of her experience, the surgeon assures you that the operation is *safe,* that ileostomy is a *rare complication,* and that the *vast majority* of patients are continent after the procedure. You think this sounds too good to be true. Moreover, what do "safe," "rare," and the "vast majority" really mean? SM has told you many times during the years how fearful he is of spending the rest of his life attached to an ileostomy bag. Can this outcome really be avoided?

The gastroenterology service, on the other hand, is furious at the surgeon for wanting to "rush" your patient to the operating room. The consultant recommends starting **immunosuppressive therapy with 6-mercaptopurine,** which he claims is highly effective both to stem the current exacerbation, allowing you to taper SM off the corticosteroids, and to prevent further episodes that would require surgery. You have never used this drug, and you worry about its associated toxicities. You have heard that it increases the subsequent risk of lymphoma. Furthermore, if this treatment works only in the short term, will SM still require surgery in the near future or can proctocolectomy be avoided forever?

As you discuss these treatment options with SM, you realize that you do not have a practical framework for weighing the risks and benefits. Not only do you lack the evidence to evaluate the potential outcomes, but you feel overwhelmed by your inability to characterize the decision. Nonetheless, since the consultants have offered contradictory recommendations and have refused to speak with one another, the decision is left to you and your patient. How will you and SM decide? *Can you make an evidence-based decision*?

INTRODUCTION TO DECISION ANALYSIS

In Chapter 1 we refined our skills of making diagnoses by addressing the probabilities of each possible diagnosis. In this chapter, we will develop a method for determining a course of action to make the *right* decision. In critical situations, such as the one in the case example above, physicians often rely on clinical judgment—their ability to make tough decisions in the face of uncertainty.

Many approaches to making medical decisions are commonly used by physicians; some of these are listed in Table 2–1. Skilled physicians intuitively make decisions on the basis of consideration of the likelihood of the possible results and the patient's preferences for each outcome. Although experienced clinicians have well-developed intuition, the

TABLE 2–1. EMPIRICAL METHODS FOR CLINICAL DECISION MAKING[1]

Dogmatism	This is the best way to do it.
Policy	This is the way we do it around here.
Experience	This way worked the last few times.
Whim	This way might work.
Nihilism	It doesn't really matter what we do.
Rule of least chagrin	Do what you'll regret least.
Defer to experts	How would you do it?
Defer to patients	How would you like us to proceed?

complexity of some decisions involves the integration of more information than the mind could possibly handle.

Optimal decision making requires that physicians identify each possible strategy, accurately predict the probability of future events, and balance the risks and benefits of each possible action, all while tailoring to the values of the individual patient. To this end, a technique called **decision analysis** was developed to assist clinicians in making rational decisions that reflect the best available evidence and the patient's individual needs.[2]

Described as a "systematic articulation of common sense"[2] **decision analysis is a formalization of the medical decision-making process.** The method of decision analysis can be thought of as a scale to weigh the risks and benefits of each potential strategy (Figure 2–1). The process is developed using a **decision tree,** a type of flow diagram that outlines the outcomes that could follow each potential decision and calculates the probability and the value of each possible event.[3]

By demanding that the clinician consider all possible consequences for the decision in question and by placing a value on the desirability of each result, the decision tree helps to diagram and structure uncertainty. Uncertainty surrounds clinical medicine: We constantly are unsure about the presence or absence of disease in a patient or about the probabilities of various outcomes of a particular treatment. In the absence of a crystal ball, decision analysis offers a technique for making a definitive choice despite the inherent conditions of uncertainty. In this chapter, we will develop a decision analysis model using a decision tree to represent our uncertainty regarding our patient SM, and we will use the results to direct our therapeutic decision.

Now that we have introduced decision analysis, when should we use this technique? Certain types of problems are best handled by decision analysis, in either a clinical situation involving an individual patient or a policy dilemma involving a population of similar patients. The following situations may benefit from the structure of a decision tree:

- **Complicated, high-stakes situations:** The presence of multiple competing risks and benefits requires a formal, quantitative method to evaluate the optimal strategy.
- **When important data are not known with certainty:** Decision analysis may reveal that a critical parameter is not well defined in the literature, rendering a single "best answer" unobtainable. Focusing the uncertainty on the missing variable rather than on the entire decision may permit a more informed choice by explicitly describing the effect of this variable on the outcome over a range of possible values.

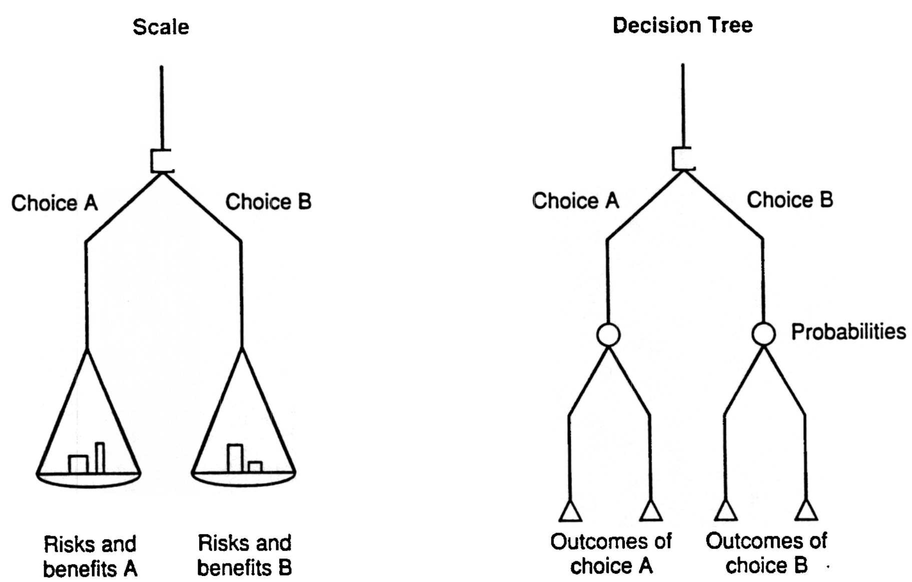


Figure 2–1. A decision tree (right) is analogous to a scale (left) that weighs the relative risks and benefits of each possible strategy.

- **When patient input is critical:** The best decision may depend heavily on how an individual patient values life with a particular disability. For our patient SM choosing between surgery and medicine, the "right" decision may be critically dependent on his personal values for the potential health outcomes he faces.
- **When important events occur at different points in time:** Many patients value the present much more than they value the future; this time preference is easily forgotten when making decisions implicitly. How do we compare death resulting from surgery today with death resulting from cancer in the distant future?

The major advantages of decision analysis arise from dividing a problem into its component parts. The method is explicit and quantitative, forcing the physician to identify all possible treatment alternatives and outcomes, to determine which data are necessary to make an educated decision, and to evaluate precisely the relative preference for each possible outcome. By providing an absolute best alternative, decision analysis is prescriptive. The decision tree does not merely represent an overview of the problem; rather, it tells us what we should do. The final product of a decision analysis model should be a rational decision made on the basis of a complete understanding of the clinical situation.[2,4]

THE FIVE STEPS OF DECISION ANALYSIS

Let's now discuss the steps to using the decision analytic technique as a tool for solving difficult problems in clinical medicine. As we outline each step, the case of SM will be used as an example of the method's application to an individual patient. These are the five steps of decision analysis:

1. Formulate an explicit question.
2. Structure the decision and make the tree.
3. Fill in the data (probabilities and outcomes).
4. Determine the value of each competing strategy.
5. Perform sensitivity analyses

Formulate an explicit question

Although this seems like an obvious step for any type of decision making, the exercise of transforming a difficult clinical situation into the form of an explicit question can be enlightening. The physician must clearly delineate all the reasonable courses of action that are available and the time frame during which the outcomes would occur. When an exhaustive list of the clinical alternatives has been made, the mechanics of structuring the decision tree can begin.

In the case of SM, the status quo is not reasonable because the situation demands an intervention. The two rational treatment interventions are surgery to cure colitis (proctocolectomy) and immunosuppressive therapy in an attempt to induce and maintain remission of ulcerative colitis (thus avoiding surgery). We will formulate our clinical question simply and explicitly:

Choose medicine or choose surgery?

Structure the decision and make the tree

The structuring step in decision analysis begins with listing the possible outcomes that could result from either strategy and ends with a completed decision tree. As a flow diagram, the decision tree should represent the logical sequence of events over time. Each therapeutic strategy may require further interventions, depending on the patient's clinical course, which should be reflected in the decision tree. For example, if immunosuppressive therapy does not improve the condition of our patient, the decision tree should indicate that he requires surgical intervention. Of course, in clinical medicine there is no limit to the potential complexity of most case scenarios; nonetheless, part of the art of decision analysis is reducing a complex decision into a finite number of straightforward components. Each aspect of the clinical scenario will eventually be defined by a choice, probability, and outcome.[3]

The drawing of the decision tree may seem unnatural for readers who are new to the concept, but with practice the tree can be as easy to use as an outline or a flow chart. We recommend that tree-building begin with envisioning the possible outcomes or health states that could result from each therapeutic strategy. When a complete list has been made of these outcomes, the outcomes should be arranged temporally to provide a representation of the time course of the clinical situation. The outcomes can then be separated into branches to represent the probability of each outcome occurring. These branches may be simply dichotomous—yes or no—outcomes (eg, "lymphoma develops" or "no lymphoma"), but the branches can also contain any number of possible outcomes. The final decision tree will result from the arrangement of these multiple branches, as we will now illustrate.

We will begin structuring our patient's decision tree by identifying the most likely outcome states of each strategy, which happen to be included in the clinical scenario. Because we are interested mostly in the long-term quality of life for SM, we will include only those outcomes that have long-term consequences. Outcomes that cause only short-term discomfort and no long-term sequelae are deliberately left out. The long-term consequences of *surgery* could be **intra-operative mortality, permanent ileostomy, permanent incontinence** (defined as daily soiling of stool), or **surgical success** to end colitis. *Medical therapy* with immunosuppressive agents may **induce remission or it may fail** because of toxicity or treatment inadequacy; thus, SM would still **need surgery.** Despite an initial period of remission, SM may experience **a severe relapse** of ulcerative colitis, forcing him to **undergo surgery at a later time.** The medicine could continue to control the ulcerative colitis, but either **colorectal cancer** or **lymphoma** may develop; SM could **survive** either of these malignant processes or he could **die.** Finally, SM may avoid surgery, experiencing **chronic ulcerative colitis,** which entails a normal life-expectancy,[5] and eventually dying of unrelated causes. A list of these final outcomes, arranged temporally, thus includes

> Surgery: immediate death, ileostomy, incontinence, surgical success
> Medicine: initial treatment failure requiring surgery, disease relapse requiring surgery, death resulting from lymphoma, death resulting from colorectal cancer, chronic ulcerative colitis

Having delineated the two treatment strategies and defined all the major possible outcomes, we are ready to construct our decision tree. Typically drawn from left to right—the decision is on the left and the outcomes are on the right—the decision tree is composed of decision nodes, chance nodes, and health outcomes. A **decision node,** represented on the tree as a square (Figure 2–2), is a crossroads in clinical medicine at which the physician must choose an action or strategy. As SM's doctor, you currently stand at a decision node until you decide on a treatment strategy.

Chance nodes, which appear as circles on the decision tree, represent events that are beyond our control; they are the uncertainty in clinical medicine. Although we cannot predict with accuracy which outcome will occur, we define the probability of each and assign these values to the chance node. The chance nodes are arranged left to right based on the temporal sequence in which the uncertainty is expected to occur. Finally, all branches of the tree must eventually reach a **terminal state,** representing one of the final outcomes. These are usually represented by a triangle in the decision tree.

Having drawn the initial decision node, dividing the tree into "Choose surgery" or "Choose medicine," let's translate our description of the surgical strategy into a decision tree format (Figure 2–3). A chance node will represent the possibility of surviving surgery or dying, death being a terminal state of the tree. Surviving surgery is followed by another chance node to identify the likelihood of the pouch procedure remaining viable ("Pouch succeeds") or resulting in an eventual ileostomy. Because the ileostomy would be permanent,

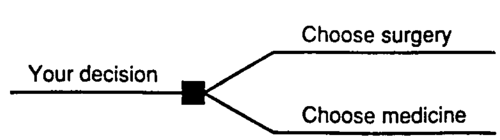


Figure 2–2. A decision node, represented by a square, indicates a clinical crossroads where the clinician must make a decision. Here, the decision must be made between medical and surgical strategies.

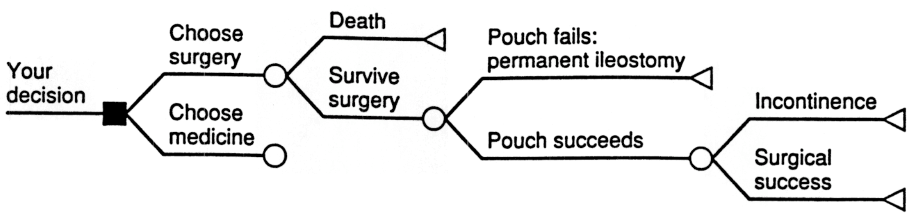


Figure 2–3 The surgery branch of the tree. The circles in the tree are called chance nodes; they represent the uncertainty in clinical medicine. In this tree, chance nodes represent the possibility of dying as a result of the surgical procedure, of being left with a permanent ileostomy, of having chronic incontinence, and of having a completely successful surgical outcome.

this branch is represented with a terminal state. The " Pouch succeeds" branch then separates into two final outcome states, surgical success and incontinence.

Although the medicine strategy appears more complicated, we can transform its possible outcomes into a decision tree by representing each possible outcome as a yes or no possibility (Figure 2–4). Thus, our first chance node is a dichotomous yes or no representing initial treatment success or failure (because of actual treatment failure or adverse effects of treatment). Treatment failure would require surgery, so we can label this outcome as "Need surgery" for now. The second chance node similarly represents the future success or failure of medical therapy to prevent a severe relapse that would require surgery.

As shown in Figure 2–4, the following chance nodes are similarly dichotomous: lymphoma develops (yes or no); if lymphoma develops, survive (yes or no). If no lymphoma occurs, colorectal carcinoma may develop (yes or no); if colorectal carcinoma develops, survive (yes or no). If treatment succeeds and malignancy does not develop (or the patient survives lymphoma), then the patient will reach the terminal state of chronic ulcerative colitis. The astute reader will notice in our tree that we have assumed that no patient will be so unfortunate as to have both lymphoma and colorectal carcinoma develop. Although possible, this occurrence is so unlikely that it is not worth including in the model.

The outcome "Need surgery" encountered in the medical tree is essentially equivalent to the "Choose surgery" subtree in Figure 2–3. Therefore, we can copy this subtree onto each "Need surgery" terminal node in Figure 2–4, except for the final one, which follows colorectal cancer. A patient with colorectal cancer will not be a candidate for ileal pouch anastomosis but will instead undergo traditional proctocolectomy, which results in a permanent ileostomy. Thus, a patient who survives colorectal cancer will have the terminal state of permanent ileostomy. Having replaced the "Need surgery" outcomes in Figure 2–4, we now have our final tree represented in Figure 2–5.

Fill in the data

Thus our decision tree is drawn. We are now ready for step 3, filling in the data. Each chance node has a probability associated with each branch that follows, and each terminal health state has a relative preference, or utility. In this step, we quantify the probability of events and the values of outcomes and insert these numbers into the decision tree.

Probability

A **probability** is a prediction of the *future*. But we must estimate the frequency of the events in our tree using evidence from the *past*. To arrive at an evidence-based solution to a clinical problem, we must derive these probabilities using the best possible information available. Major sources of probability that we can incorporate into a decision analysis include

- Clinical studies
- Clinical databases
- Expert opinions and educated guesses

Clinical studies. Medical literature probably provides the most reliable source of evidence because the data are quantitative and the studies presumably peer-reviewed.[2] The methods for evaluating the medical literature described in Section 3 of this book will help you determine

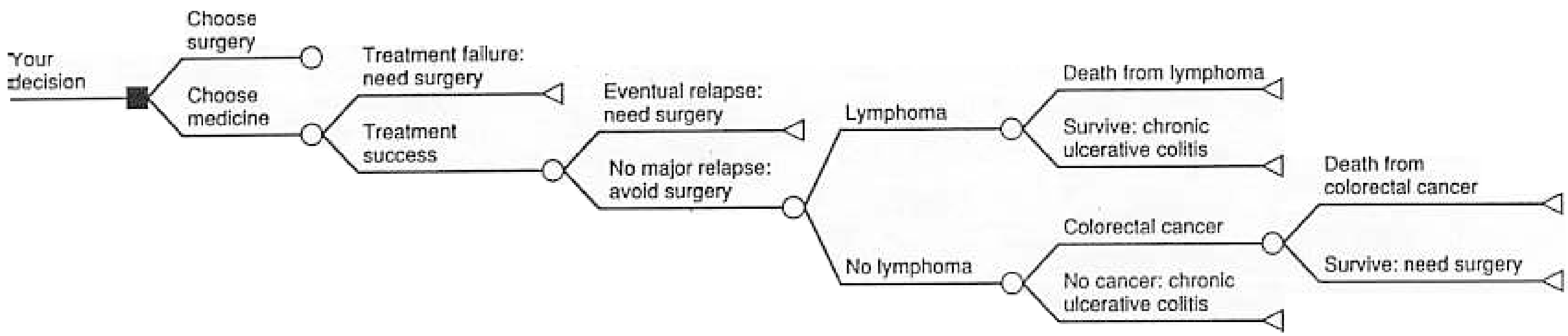


Figure 2–4. The medicine branch of the tree.

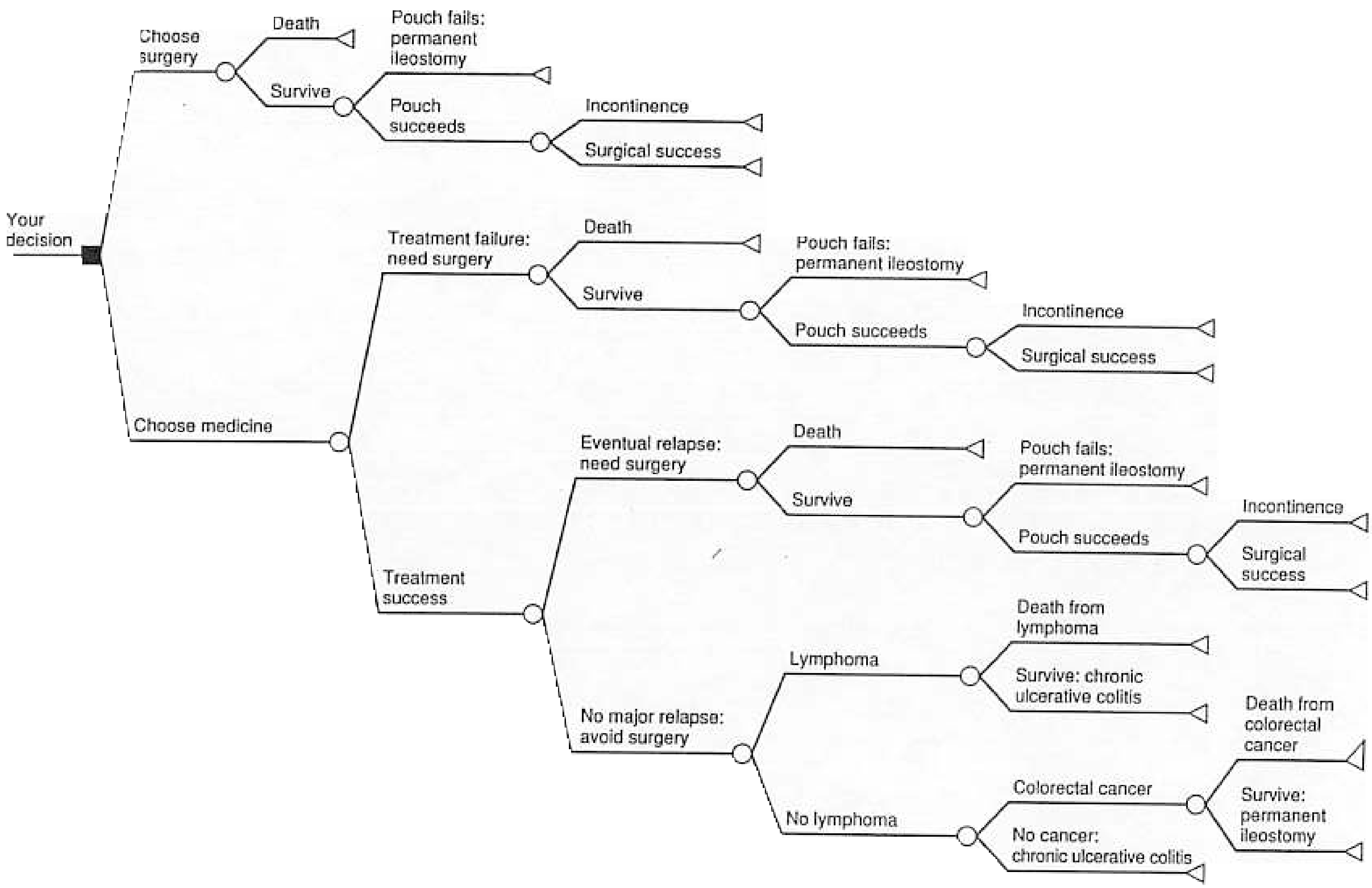


Figure 2–5 The final decision tree. Although this tree appears complex, it simply combines the surgery and medicine trees drawn in Figures 2–3 and 2–4.

the validity of these sources of data. Even if published information is valid, however, it may not be applicable to your patient. The study population may be different, the treatment may have changed, a new test may be available, or a surgical technique may have been improved. As in applying any source of published literature to an individual patient, care must be taken in constructing a decision tree to ensure that the published probability applies to the clinical situation at that chance node. Using a poor source of evidence can be less valid than having no data at all.

Clinical database. Local patterns of disease or outcomes of treatment are often more relevant than published clinical studies. For example, the complication rate of patients undergoing ileal pouch anastomosis for the particular surgeon at your hospital is more applicable to your patient than the rate published in a peer-reviewed journal. For our hypothetical patient and for the purpose of generalization, the surgical complication rate for this procedure will be taken from published literature.

Expert opinions/educated guesses. Often we cannot find adequate data to provide an evidenced-based estimate for a chance node. Rather than incorporate data that are not truly applicable to the clinical situation, it is preferable to seek the opinion of one or more experts—the "educated guess." In the absence of an evidence-based approach, this intuitive method would be the entire basis for decision making. But by structuring the problem with decision analysis, we can limit the "guess" to the probabilities of one or two specific events. The accuracy of the subjective probability is of course dependent on the experience of the individual making the estimate; however, the ability to derive probabilities is a teachable skill that is crucial to the practice of evidence-based medicine (see Chapter 1, discussion of heuristics). The importance of the "educated guess" to the overall decision can be determined via sensitivity analysis, as discussed in step 5 on page 48.

We will now address the probabilities in our decision tree using available evidence. We learned in Chapter 1 that the sum of all probabilities must add up to 1.0 and that we can revise probabilities to adjust for added information. The probabilities in Table 2–2 were obtained by a thorough review of the literature, using the techniques described in Chapter 5 on searching MEDLINE. The notation p[outcome] in this table stands for the probability of that outcome occurring. You will note that the sum of the probabilities placed around each chance node equals 1.0.

Note that no increase in the risk of lymphoma was found among patients with ulcerative colitis who received 6-mercaptopurine. Although the risk of lymphoma is not zero, as suggested in Table 2–2, this branch can be eliminated from the decision tree because the risk is

TABLE 2–2. PROBABILITY ESTIMATES FOR EACH CHANCE NODE IN THE DECISION TREE.*

Probability Variable	Estimate	Reference No.
		6
		7
		6,7
		8,9
		9
		10
		10
		9
		9
		11,12,13
		11,12,13
		13
		13

* p[event] = the probability of the event occurring.

the same whether the patient receives surgical or medical therapy. The incidence and survival rates of colorectal cancer are based on patients who received active surveillance with colonoscopy, as documented in the reference. The only probability that is not explicitly derived from clinical literature is the probability of eventual relapse requiring surgery. The long-term efficacy of chronic immunosuppressives in avoiding surgery has not been extensively studied. We therefore consulted an "expert" gastroenterologist for an educated estimate of this probability. A similar estimate was found in the referenced article.

Valued outcomes

As our clinical scenario has demonstrated, the range of possible outcomes for an important clinical decision may be broader than just life or death. To compare the results of clinical strategies, a method for ranking outcomes must be devised. How would levels of disability, discomfort, or inconvenience be ranked? These values must be considered as rigorously and quantitatively as our sources of probability if our analysis is to be valid. The most commonly used method of ranking health states in medical decision making is called utility assessment.

Utility = a quantitative measure of the strength of a
patient's preference for a particular state of health or outcome

Utilities are the currency used to trade among possible outcomes. Because the individual patient determines utility, utilities are appropriately and necessarily subjective and are essential to the decision tree.[3] Alternative outcomes to utilities could include life expectancy,[14] functional status, or satisfaction. We, however, will focus on utility.

The first step in assigning a quantitative utility to an outcome state is to rank the outcomes from most desirable to least desirable. Our patient SM states that the most desirable outcome would be a cure of his ulcerative colitis to avoid all medications and worry, yet avoiding the surgical complications of incontinence or ileostomy; in other words, **surgical success** is his best outcome. Next best would be prolonged remission resulting in asymptomatic **chronic ulcerative colitis** that avoids surgery and does not result in colorectal cancer. The third best option is surgical cure of ulcerative colitis that leaves him with the nuisance of being somewhat **incontinent** but without an ileostomy. The fourth best option is surgical cure that results in a **permanent ileostomy.** The outcome of **colorectal cancer–related death** is almost the worst option. The worst possible outcome, though, is immediate **surgery-related death.** Remember, these are the rankings of one individual patient. They reflect his values alone.

Let's now list these ranked outcomes from 1 to 6:

1. Surgical success
2. Chronic ulcerative colitis
3. Postsurgical incontinence
4. Permanent ileostomy
5. Colorectal cancer–related death
6. Surgery-related death

Ranking the outcomes from 1 to 6 helps us understand SM's preferences for the possible outcomes of our decision, but for decision analysis this is insufficient. Where does ileostomy fall on a continuum of death to perfect health? Would future death resulting from colorectal cancer be valued akin to immediate death or be closer to permanent ileostomy? We need to quantify the patient's preference for each of these outcomes if we are to continue with decision analysis.

Because utilities are quantitative measures, they require a scale, which is determined arbitrarily. For convenience the scale usually is 0–1.0, with 0 being the worst possible outcome (eg, immediate death) and 1.0 being a state of perfect health relative to the particular patient. All other outcomes are valued with a utility somewhere between these two extremes, depending on the patient's preference. The techniques for deriving an individual's personal utilities arise from basic economic theory. The fundamental assumption is that individuals will behave rationally in order to maximize their personal satisfaction or utility.

The methods for determining an individual's utilities, described below, are tools for forcing the patient to reveal his or her preferences for potential outcomes; thus, the decision analysis is tailored to fit the patient's own values.

We will focus on three common methods for calculating personal utilities:

- Visual analog scale
- Time trade-off
- Standard gamble

Visual analog scale (interval scaling). This method for determining utilities relies on the patient's ranking of health states using a linear scale. The scale (basically a ruler) is presented to the patient with a health state at either end. The patient demonstrates his or her relative preference for an intermediate outcome, relative to the health states at either end, by marking the line at the desired point. Using this example, we might ask our patient SM to mark the line where he would value an ileostomy, if surgery-related death = 0 and surgical success = 1.0.

Incontinence
(0) - Surgery-related death ———————— X ——— Surgical success - (1)

If he chose a point three-fourths of the distance between 0 and 1.0, as shown in the example above, his utility for incontinence would be 0.75. Similarly, the value of another intermediate outcome (eg, ileostomy) may be scaled by repeating this technique.

Ileostomy
(0) - Surgery-related death ———————— X ———————— Surgical success - (1)

The primary problem with this method is that it may bias results toward the middle of the scale, so utilities may be scored inappropriately low. Rarely would an X be placed at 0.98, for example, because persons tend to avoid marking the extremes of a scale.

Time trade-off. This technique involves presenting the patient with a trade-off between the quality of his or her life and the length of life in time. The assumption is simply represented for health states A and B, where A is perfect health and B is a less desirable health state:

$$\text{Time A} \times \text{Utility A} = \text{Time B} \times \text{Utility B}$$

Time trade-off thus establishes that 10 years lived with utility 0.5 are equivalent to 5 years lived with a perfect utility of 1.0. We can use this framework to help our patient reveal his or her personal utilities for each possible health state.

For the equation above, Utility A (perfect health) is 1.0 and Time B is the maximum possible life expectancy (we'll use 10 years in this example). By choosing a quantity for Time A that is some fraction of Time B, the patient will define his or her personal value for Utility B. To illustrate this concept, let's return to our patient SM. You define A as relative perfect health (for SM this would be the health state "Surgical success") and B as life with an ileostomy. You can now frame the question to SM as follows:

> If you were faced with a future lifetime of 10 years (Time B = 10) with an ileostomy (Utility B), how much time (t) would you be willing to give up to spend your life in perfect health (Utility A)?

By framing the question in terms of "giving up" time, we have introduced the variable t, where

$$\text{Time B} - t = \text{Time A}$$

If SM states that he would give up or trade 1 year, then $t = 1$ year and Time A = 9 years. Returning to our original equation, the utility of the ileostomy (Utility B) can be solved easily:

$$\text{Time A (9 years)} \times \text{Utility A (1.0)} = \text{Time B (10 years)} \times \text{Utility B}$$

Solving for Utility B, we find the value to be 0.9. Thus, SM has revealed his personal utility for ileostomy to be 0.90. This method can be repeated for each of the intermediate health states.

Standard gamble. Probably the most commonly used and explicit form of utility assessment, this technique involves forcing the patient to choose between (1) accepting a certain health state and (2) taking a gamble to achieve a better outcome, while risking the possibility of the worst outcome.

An analogy for the standard gamble is the "Let's Make a Deal" game show, played for high stakes. The contestant (your patient) must choose between two doors. Door 1 is open so the contestant sees a certain outcome; this outcome is an intermediate health state whose utility needs to be defined. Door 2 is closed. Behind it may be the most desired outcome (perfect health), but this door also may hide instant death. Whether the contestant chooses door 1 or door 2 is dependent on the probability that door 2 holds perfect health versus the probability of instant death. The contestant will decide the value for the probability of finding a perfect outcome behind door 2 that makes door 1 and door 2 equally appealing. Using this situation, we can determine the patient's personal utility for the intermediate health outcome that appears in door 1.

Assume that behind door 1 is a certain outcome of permanent ileostomy; behind door 2 is either the best outcome, surgical success [utility(2a) = 1.0, probability(2a) = q], or immediate death [utility(2b) = 0, probability(2b) = 1–q]. For what probability (q) would SM be indifferent between the two doors?

Door 1: Ileostomy [probability = 1.0] [Utility = ?]
Door 2: Surgical success [probability (2a) = q] [Utility (2a) = 1.0]
or
Immediate death [probability (2b) = 1 – q] [Utility (2b) = 0]

As in the time tradeoff model, we can represent the choice with a simple equation:

$$[p(1) \times U(1)] = [p(2a) \times U(2a)] + [p(2b) \times U(2b)]$$

Since $p(1) = 1.0$, $U(2a) = 1.0$, $U(2b) = 0$, $p(2a) = q$, and $p(2b) = 1-q$, then $U(1)$ can be represented as:

$$1.0 \times U(1) = [q \times 1.0] + [(1 - q)) \times 0]$$

which reduces to:

$$U(1) = q$$

As shown, the equation simplifies to U(1), the utility of the ileostomy, being equal to q, the probability of finding surgical success behind closed door 2. With help from the physician, the patient will determine the value of q, or conversely (1 – q)—the risk of immediate death—which makes the choice between the two doors a "toss-up." At this value, q is equal to U(1), the utility of the intermediate outcome. Thus, the patient defines his or her utility for this outcome. Below, we will demonstrate how the physician can lead the patient through the standard gamble.

Each of these three methods for utility assessment has its relative merits. In addition, the methods have been shown to produce different results, although controversy surrounds the question of which result is most valid.[15] The visual-analog scale is the most intuitive for patients to understand, yet may bias toward lower values, as already mentioned. The time trade-off compares certain outcomes, which for some patients makes the time trade-off more comprehensible than the standard gamble.[16] The standard gamble, however, involves an element of risk that may be more realistic, yet can be difficult for some patients to understand. Use of both of these latter two methods would be valid in this decision analysis.

Although you could use either the standard gamble or the time trade-off for your patient, you decide to try the standard gamble method of utility assessment because it seems to reflect the element of risk involved in this clinical situation. You return to SM and outline the potential health states behind the two doors. You offer him the gamble with q = 0.75:

> Would you choose door 1, the certainty of an ileostomy, or would you choose door 2, gambling for the 75% chance of surgical success, while risking a 25% chance of instant death?

SM chooses door 1, the certain ileostomy, as he is unwilling to accept a 25% chance of immediate death. You increase the likelihood of surgical success to 85% and 90%, yet he still chooses door 1, the certain ileostomy. At a 95% chance of surgical success, SM states he would definitely choose door 2, risking a 5% chance of death to avoid the certain ileostomy. As you offer percentages between 90% and 95%, SM reveals that he is indifferent to the two doors at q = 92%. Thus, his utility for the outcome of ileostomy is 0.92. Repeating this process for the two states between ileostomy and surgical success reveals that SM values chronic ulcerative colitis (with the continued fear of cancer) at 0.98 and a state of postsurgical incontinence at 0.95.

The health-state of cancer-related death is more difficult to quantify because the outcome occurs in the distant future. Your review of the literature revealed that the incidence of colorectal cancer in patients with ulcerative colitis may be represented as a symmetric bell-curve, with a peak in mortality at age 55.[12] As a 40-year-old man with a life expectancy of approximately 30 years, SM would lose an average of half his life expectancy if he were to die of colorectal carcinoma. You return to the standard gamble and ask SM the following question:

> Assume that door 1 holds a certainty of 15 years of life followed by death resulting from cancer. Behind door 2 might be a normal life expectancy of 30 years in perfect health (probability = q, utility = 1.0) or immediate death (probability = 1 − q, utility = 0). For what probability (q) of finding a normal life expectancy behind door 2 would you be indifferent between door 1 and door 2?

You are surprised when he chooses a probability for perfect health, and thus a utility of cancer-related death, of 0.7. You expected SM to make q, and thus the utility of cancer-related death, equal to 0.5 because this outcome of a life expectancy of 15 years is the midpoint between instant death and a life expectancy of 30 years. We will continue discussing time preferences later. You have now assisted SM in calculating his personal utilities for the possible outcomes of the decision tree:

Surgical success = 1.00
Chronic ulcerative colitis = 0.98
Postsurgical incontinence = 0.95
Permanent ileostomy = 0.92
Colorectal cancer–related death = 0.70
Surgery-related death = 0.00

The standard gamble technique may seem like a strange method for generating patient utilities, but in reality our patient does take a gamble by undergoing the risk of surgery to reap its possible benefits. By responding to the forced choices of the standard gamble, SM has revealed the relative strengths of his preferences for these possible outcomes, which we can now incorporate into our decision tree. Notice how these quantitative utilities differ from a simple, ordinal ranking of 1 to 6.

Before we move on to calculating the results of our decision tree and determining the expected values of each arm of the tree, we should note a few shortcomings of utility assessment:

- An individual's preferences may vary with time. An ability that seems highly desirable at a young age (eg, the ability to run fast) may be less important later in life.
- A patient usually has a limited understanding of the potential outcomes that he or she has never experienced. Notice that SM has an emotional aversion to ileostomy, causing him to value the outcome at 0.92. A patient who actually lives with an ileostomy or incontinence may adjust to these lifestyles and rank them with a much higher utility.

- Some patients may be incapable of understanding and participating in these tradeoff and gambling techniques. In these patients, quantifying utilities can become problematic.
- Physicians may impose their own values on utility assessment, biasing the values away from the patient's true preferences.[2]

Determine the value of each competing strategy

After inserting the estimated probabilities and utilities of each possible outcome, we now analyze our completed tree to answer our original question, "Choose surgery or choose medicine?" The method of analyzing the decision tree is known as **expected value decision making.** We will review the "Choose surgery" portion of our decision tree (Figure 2–6) to demonstrate expected value calculations.

To calculate the expected value of a decision tree, we begin at the end of the tree and work backward, chance node after chance node, until we arrive at the beginning. The expected value of a chance node is the sum of each of its branch's probability multiplied by its utility; in other words, a weighted average of the node. The terminal branch of the "Choose surgery" section of the tree is characterized by a 0.82 probability of surgical success (U = 1.0) and a 0.18 probability of permanent incontinence (U = 0.95). To predict the average outcome, or the expected utility, we multiply

$$0.82 \times 1.0 + 0.18 \times 0.95 = 0.991$$

This calculation is called **averaging out** the chance node; its expected value is 0.991 (represented in Figure 2–6 within a rectangle adjacent to the final node in the surgical subtree). The next chance node we encounter, moving backward along the tree, involves a probability of 0.07 for an ileostomy (U = 0.92) and a probability of 0.93 of no ileostomy (expected value = 0.991, as calculated above). The expected value of this chance node is equivalent to

$$0.07 \times 0.92 + 0.93 \times 0.991 = 0.986$$

This process of working backward along the tree to determine the expected value for each arm of the tree is called **folding back** the decision tree. Practice calculating the expected value of different chance nodes using Figure 2–6, which shows the entire averaged out and folded back decision tree. The tree ultimately tells us to choose the surgical procedure because its expected utility is higher—0.984 versus 0.976.

Often, the difference between two strategies in a decision tree will appear to be small, as in this case. However, this result still reflects the optimal choice for the decision that SM faces. If the decision is structured as accurately as possible and the best possible values for probabilities and utilities are incorporated into the tree, the results of the analysis should be accepted. In this example, surgery is the rational choice.

Perform sensitivity analyses

Despite the confidence one may have in the completed decision tree, skepticism may remain regarding the results of the analysis. We might be concerned about the effect of a particular probability estimate that is based on inadequate data or one that represents the most dreaded outcome. Or, we may worry that a particular utility estimate has overly influenced the final results. To address our fears regarding the reproducibility of the conclusions and their dependence on any particular piece of datum, we turn to sensitivity analysis.

Sensitivity analysis tests the stability of an analysis over a range of probability estimates and value judgments. The process challenges the conclusions by systematically varying the values of particular probabilities and utilities used in the decision tree. The range selected should correspond to the reasonable area of uncertainty around each estimate. This enables us to assess the stability or "robustness" of the end result and determine whether the decision hinges on a particular variable.

In its simplest form, sensitivity analysis involves altering a single variable along a range of probabilities or utilities and recalculating the expected value of each strategy at each probability. Because only a single variable is varied, this form is called **one-way sensitivity**

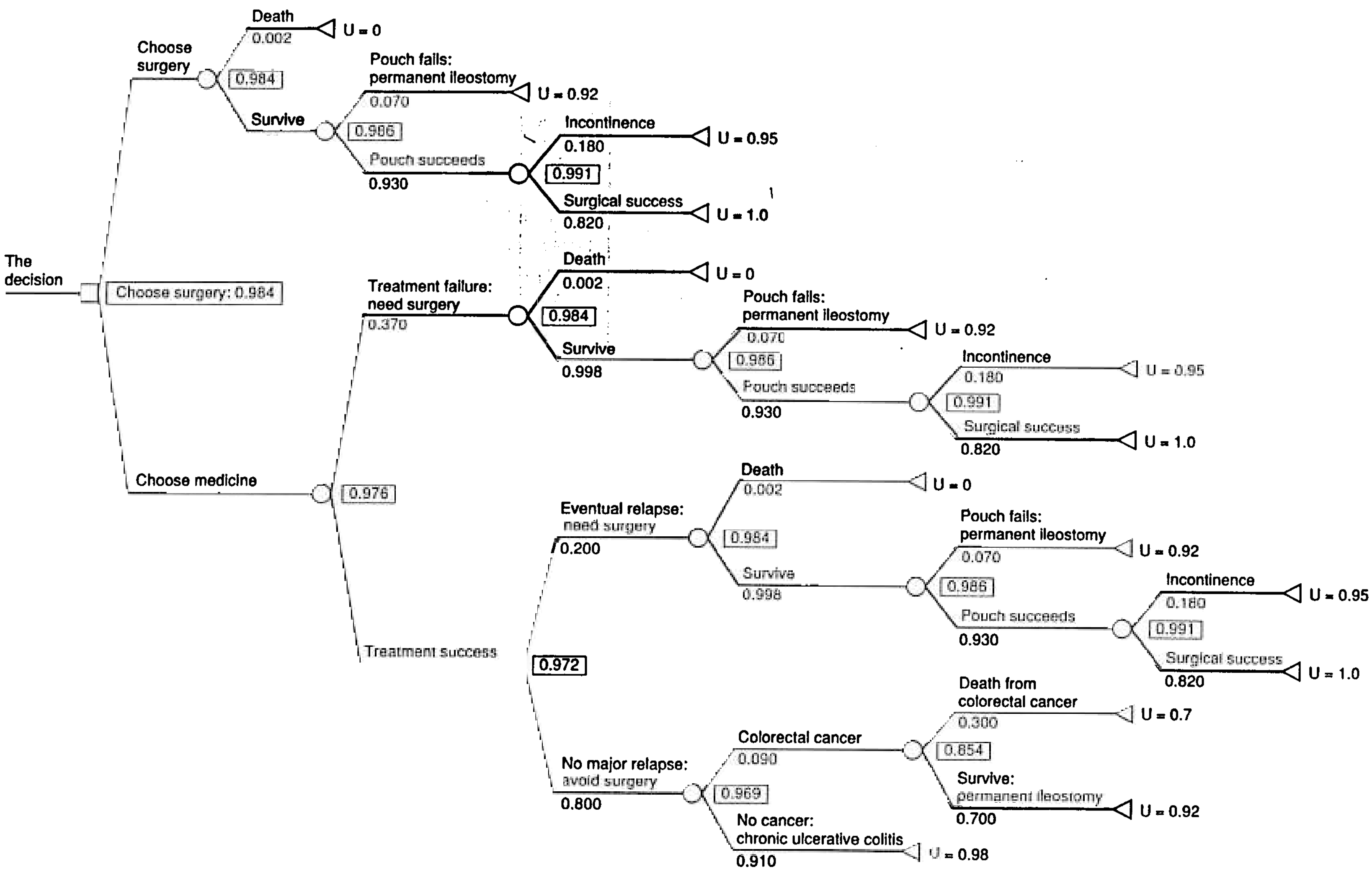


Figure 2–6. Averaging out and folding back of the decision tree. In this view of the decision tree, we see all the data needed to determine the preferred strategy. The probability for each of the branches that follows a chance node is shown beneath the branch. The utility of each terminal state is shown following its representative triangle. Knowing the probability of each branch and its utility allows us to calculate the expected value—or "average out"—each decision node from right to left (refer to description in text). The expected value of each chance node is shown in the rectangle adjacent to the node.

analysis. The expected values (in this case, expected utilities) for the surgical and medical treatment arms calculated over the wide range of possible probabilities of dying during surgery (p[surgery-related death]) are plotted in Figure 2–7.

The x-axis displays the range of values for the probability of this outcome and the y-axis shows the expected value of the "Choose surgery" and "Choose medicine" strategies at each point. Our reference estimated the risk of death to be 0.002, or 1 death per 500 cases. One-way sensitivity analysis shows that surgery is preferred over medical therapy if the risk of surgical mortality is less than 0.009, or 1 death per 111 cases. This point at which the two lines cross is called the **indifference point,** or **threshold.** Thresholds in medical decision making are discussed in detail in Chapter 3.

A second plot, Figure 2–8, represents a one-way sensitivity analysis of the probability of developing cancer (p[cancer]). We made a relatively low estimate for the likelihood of this event, 0.09, based on active surveillance with routine colonoscopy.[13] One-way sensitivity analysis reveals that surgery is the preferable strategy unless the probability of cancer developing is less than 0.04. Sensitivity analysis was repeated for the other probabilities and utilities in the decision tree, as seen in Table 2–3. Surgery had a higher expected value than medical therapy within a wide range of values for each variable.

The results of these one-way sensitivity analyses are reassuring, as they tell us that our conclusion does not hinge precariously on any one of our estimates. For example, the rate of surgical mortality in Figure 2–7 would have to be four times higher for the medical therapy to be superior. We also find that the one probability arising from expert opinion and not directly from medical literature, the probability of future relapse requiring surgery, has no impact on the overall conclusion (surgery is better than medicine for all possible values). In fact, none of the thresholds in Table 2–3 appears to be close to the "best estimate" incorporated into the decision tree. Sensitivity analysis of probabilities is more important than it is for utilities in an individual's decision tree, since the patient determined his own utilities.

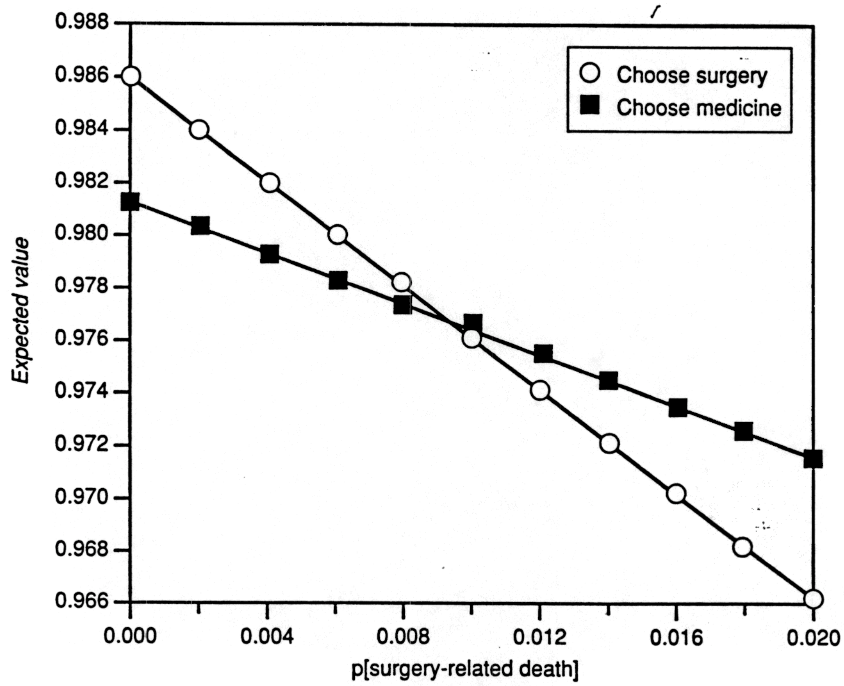


Figure 2–7. One-way sensitivity analysis of the variable p[surgery-related death], the probability of the patient dying from surgery. The effect of varying the probability of surgical mortality on the expected value of the surgery and the medical strategies is shown. Our original estimate for p[death] was 0.002. According to this figure, surgery remains preferable to medicine when p[death] is less than 0.009, the threshold value. If p[death] is greater than 0.009, medicine is preferable to surgery.

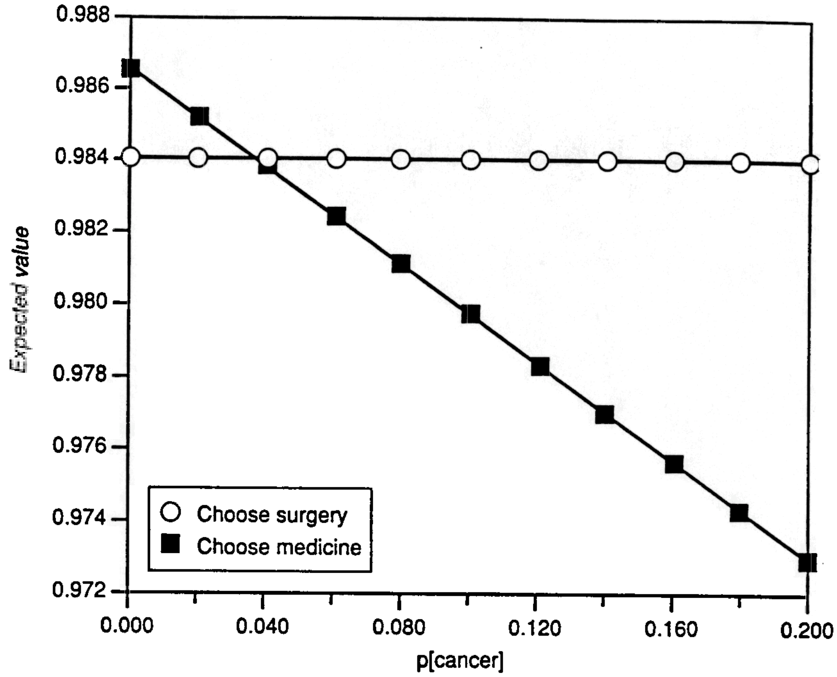


Figure 2–8. One-way sensitivity analysis of the variable p[cancer], the probability of colon cancer developing. Notice that the expected value of the surgery strategy is not affected by the probability of the development of colon cancer because proctocolectomy prevents colon cancer. We chose 0.09 as the best estimate for the likelihood of colon carcinoma developing in our patient. Above the threshold of 0.04, the surgery strategy is still preferred. For p[cancer] less than 0.04, the medicine strategy is preferred.

These utilities are inherently valid for this patient unless we misled the patient during utility assessment. When you read published decision analyses, addressed in Chapter 10, evaluating the utilities with sensitivity analysis becomes more important because you will need to determine whether your patient's personal values would change the results reported in the article.

Two-way sensitivity analysis can be used to analyze the effect of two variables simultaneously over every possible combination of values.[4] The graph of this type of plot indicates the combination of probabilities for which each strategy is preferred. In our analysis, the most crucial variables are the rates of surgical mortality and of colon cancer developing, as these probabilities are associated with the most dreaded outcomes and the lowest utilities.

TABLE 2–3. ONE-WAY SENSITIVITY ANALYSES TO TEST THE IMPACT OF EACH PROBABILITY AND UTILITY ESTIMATE ON OVERALL OUTCOME OF THE DECISION TREE.

Variable	Best Estimate	Threshold	Choose Surgery	Choose Medicine

U[outcome] = the utility of that outcome; Best Estimate = the value for that variable incorporated into the decision tree (considered to be most representative of the true value for the probabilities and of the patient's actual preference in the case of utilities); Threshold = the value of that variable for which surgery and medicine strategies are equivalent (above and below the threshold value, one of the two strategies is preferred, as seen in the two far-right columns).

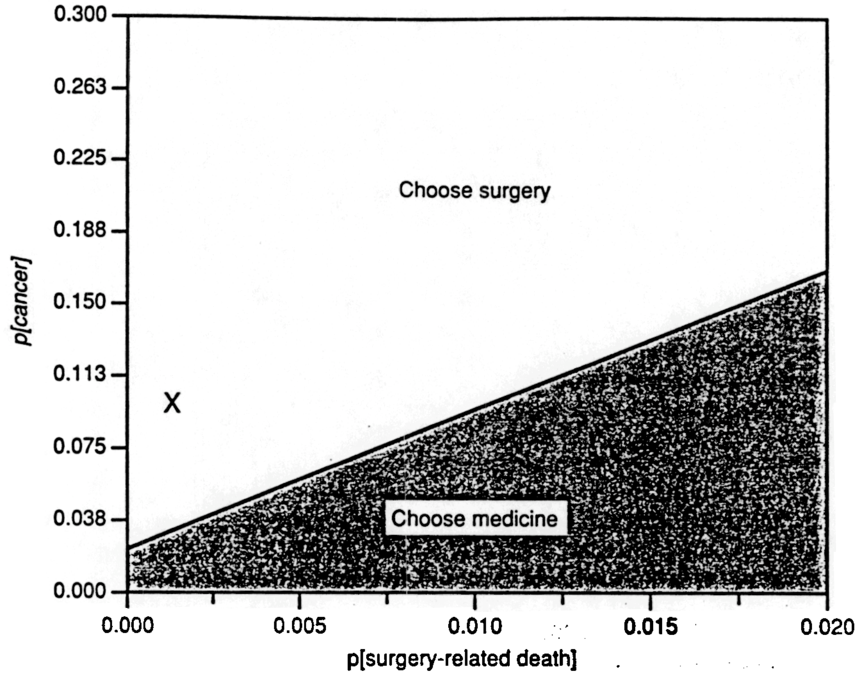


Figure 2–9. Two-way sensitivity analysis reveals the effect of altering the value of two variables simultaneously. On the x-axis is p[surgery-related death], the probability of surgical mortality. We recall from Figure 2–7 that surgery loses its advantage over medicine as p[surgery-related death] increases. On the y-axis is p[cancer], the likelihood of colon cancer developing. Figure 2–8 demonstrated that the value of the medicine strategy declines steadily as p[cancer] increases. With two-way sensitivity analysis, we may choose any two values for p[surgery-related death] and p[cancer] and determine the preferred strategy. Above the dividing line, surgery is the preferred strategy, and below it, medicine would be optimal. Our best estimate—p[surgery-related death] = 0.002 and p[cancer] = 0.09—is indicated with an X.

Two-way sensitivity analysis on these two variables is shown in Figure 2–9. Notice that as the risk of surgery-related death increases along the x-axis, medical therapy is favored; conversely, as the risk of cancer rises along the y-axis, surgery becomes preferable. Although these calculations and plots can be tedious to construct by hand, they can be created in seconds using a decision analysis software program (discussed later in this chapter).

Sensitivity analysis is a crucial step in decision analysis to test the effect of the probabilities and utilities that impact the model. The uncertainties that have the greatest impact on the decision can be investigated further to obtain more reliable estimates; thus, sensitivity analysis can help direct future research. If the results of a decision analysis are to be communicated, as in a published study, sensitivity analysis must demonstrate to the reader the stability of the conclusions. When the results of our analysis remain valid over a wide range of probabilities, we have even more confidence in the conclusions. However, in a decision analysis that we perform using our best estimates of probabilities and utilities for our individual patient, we must make a decision regardless of sensitivity analysis, and we must be prepared to accept the results of the decision tree.

ADVANCED METHODS OF DECISION ANALYSIS

Time preferences

One of the most complex aspects of decision analysis is the handling of preferences over time. We mentioned earlier that a patient's values for certain outcomes may change over time. People also value health states differently from the present to the future, usually devaluing the future relative to the present. Most would not trade a year of perfect health now for one 15 years in the future. We saw an example of this in our decision tree when our patient SM placed a utility of 0.7 on the outcome of cancer-related death, which would have decreased his life expectancy by about half. We might have expected a utility of 0.5 for this outcome, but SM showed that he was not willing to risk the near future for the promise of a lengthened life expectancy. SM, like most people, values the present greater than the future.

Placing a lower value on the future compared with the present is called **discounting.** Discounting is a systematic method for devaluing the utility of health in the future relative to the present. A standard rate of discounting used in published studies incorporating quality of life and time is 3%. Thus, a year with a given health state X is devalued by an annual rate of 3% for each year from the present in which it occurs. The formula for discounting a year in a health state, with utility = U and discount rate = D, in years (y), for example, is[17]

$$U/(1 + D)^y$$

Therefore, with a discount rate of 3%, a year spent in perfect health 10 years from now is assigned a utility:

$$1/(1 + 0.03)^{10} = 0.744$$

This year is valued at 0.744, relative to the same year in the present.

Discounting applies to money as well as to utilities, as discussed in Chapter 4. In decision analysis, the importance of discounting was recognized from observed behavior among patients who were unwilling to accept the short-term risks of a procedure (eg, surgery), although they would enjoy an overall long-term benefit in life expectancy or quality of life. A method was required to scale down these future benefits into meaningful units that we can use today. Although 3% is often used as a standard estimate, individual patients have their own intrinsic discount rates that shape their personal values of the future, relative to the present. These rates can be derived for use in an individual's decision analysis.[18,19]

As we discount utilities over time, we must also account for the amount of time that is spent with each value of utility. In clinical research, the unit of measure most used for the accounting of utilities over time is the **quality-adjusted life year, or QALY.** A QALY is simply calculated by multiplying the time in years by the quality as measured in utilities. For example, 5 years spent in a health state of utility 0.6 is equivalent ($5 \times 0.6 = 3.0$) to 3 years spent in perfect health, or 3 QALYs. These QALYs can then be discounted depending on how far into the future the year occurs. QALYs are used frequently in cost-effectiveness analyses and are discussed in greater detail in Chapter 4.

Markov process

Some cases in clinical medicine are too complicated to be modeled by the simple tree structure we used for our patient with ulcerative colitis. The linear structure of a standard decision tree may be incapable of representing the natural history of a complex disease. For example, to characterize the prognosis for a woman with moderate coronary artery disease, we would need to incorporate the possibility of future events at distant points of time and the gradual progression of the disease. A simple tree would have difficulty handling the complexity of time for this type of medical decision making and could not give an accurate estimate of life expectancy. The Markov model is an important method of modeling events that may occur in the future by creating a basic tree structure that cycles over fixed intervals of time.[20] For these more complex models, computer software is essential.

As in the more basic decision tree, a Markov model begins with a patient facing a difficult decision or receiving a diagnosis of a chronic disease. The model then defines a series of health states through which the patient may transition. A patient who receives a diagnosis of a hypothetical disease X may have the possible health states shown in Figure 2–10 (well, ill, and dead). The arrows in the figure demonstrate the possibilities for movement between these states. For this disease, a well person can become ill during each period or cycle, and a well or ill person could transition to death. However, once a person becomes ill with this hypothetical disease, he or she can only stay the same or die during each consecutive cycle of time.[20,21]

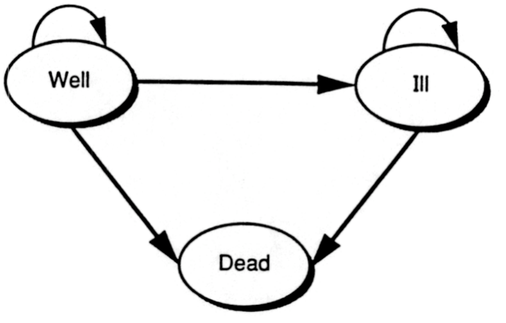


Figure 2–10. Diagram of the Markov states demonstrating the possible transitions among the health states of a chronic disease. Notice that a well person can either become ill or die. But once a person proceeds to the ill state he or she cannot return to well. Death is an absorbing state, so no person can leave this health state.

There are three types of health states in a Markov model:

1. Dynamic states: Transition is possible into one of the other states, including itself.
2. Temporary states: Outward transition is mandatory; a person cannot remain in the same state.
3. Absorbing state: No transitions can occur, ie, death.

During each cycle of the Markov model, usually 1 year, a patient has a defined probability of transitioning from his or her health state into one of the other possible states or remaining in the current state. The **Markovian assumption** is that these transition probabilities remain constant with each cycle through time. The model may continue until the patient (or cohort of patients) reaches an absorbing state, ie, death, or may continue for a fixed number of cycles.[4]

Each of these health states has a defined utility, and the computer software calculates the amount of time the patient spends in each health state. Thus, as we learned above, the software can add up the QALYs that each patient accumulates as he or she cycles through the transition states of the model, year after year, until eventual death. What's more, these QALYs can easily be discounted each cycle into the future to adjust their value to present day units. The strategy that accumulates the most QALYs (highest expected value) is the optimal choice in the decision analysis.

The Markov model is certainly more complex than the standard decision tree and may be more difficult to apply to the case of an individual patient. However, it involves the same five steps as the simple decision analysis above and the decision trees look similar. Moreover, the model is relatively easy to execute with the help of a computer and may offer important insights. The Markov model is especially useful for modeling a disease process over time and the effect of possible interventions on the progress of the disease. To answer questions regarding public health, one can simulate clinical trials with decades of follow-up that would not be feasible to conduct.[22] For a more in-depth review of the Markov process, the reader is referred to a number of excellent published reviews.[2,3,21]

Computer software in decision analysis

Decision analyses applying to individual patients, like the model we constructed in this chapter, can usually be executed with a hand-held calculator. However, several software programs have been developed to facilitate the process. These programs provide the framework for the decision tree or Markov model and can rapidly graph the results of sensitivity analysis. In addition, each is accompanied by a manual that directs the user through a sample decision analysis. As decision trees become more complex and advanced models are created, computer assistance becomes mandatory. The following software packages are frequently used by clinical researchers:

- SMLTREE (J. Hollenberg, New York, 1991)—available in PC only.
- DATA (Decision Analysis by Tree Age, Tree Age Software Inc, 1995)—available in Macintosh and in PC.

LIMITATIONS OF DECISION ANALYSIS

Most of this chapter has focused on the advantages and the strengths of decision analysis as a method for clinical decision making. But you may ask, "If decision analysis is so great and rational, why don't physicians use it more?" Let's examine five reasons why.

Clinical medicine is very complex

Often patients have multiple medical problems, making many clinical studies inapplicable to their case. It may seem very difficult to reduce "real life" into a list of outcomes that fits into a decision tree. Incorporation of new tests and therapies into an analysis may be difficult in the absence of data validating their efficacy. All these factors make clinical medicine more challenging; thus, in these situations decision analysis is more difficult, but also more necessary as an alternative to the traditional forms of clinical decision making.

The method can be laborious

Undoubtedly, decision analysis can be time-consuming, especially if a review of the literature is necessary as it was in our patient with ulcerative colitis. In an urgent and anxious situation, there may not be time or patience to complete the process. Nonetheless, the wheel need not be reinvented for each patient. Once we have structured a decision tree and gathered all the necessary clinical information, we can adapt it to similar patients in similar situations. A gastroenterologist may encounter our clinical scenario several times a year. Individual preferences need to be re-elicited and some likelihoods may bear revising, but the tree remains ready for use.

Most clinicians have limited experience with the method

This formidable obstacle is slowly being reduced. This chapter is meant to entice future experimentation and utilization of decision analysis. Excellent textbooks on the subject are included in the references at the end of this chapter.

Decision analysis cannot be performed in the absence of evidence

Clinical situations arise in which there is no evidence to direct a decision. Completing the five steps of decision analysis would be very difficult in these instances, but the techniques of formulating an explicit question and structuring the problem can still be helpful in the absence of data. In fact, sensitivity analysis may reveal that the missing data have no impact on the final decision. The skill of deconstructing a complex decision into manageable probabilities will improve "clinical judgment" to arrive at the best possible decision.

Preferences may be difficult to elicit and may change over time

As discussed previously, some patients may have difficulty revealing their preferences quantitatively. Relative preferences for certain outcomes may evolve with age. These obstacles are challenging to overcome and have varying impact on the results of the decision analysis. Sensitivity analysis can help to demonstrate the impact of the utility on the conclusion.

SUMMARY

1. Decision analysis is a rational method for medical decision making that incorporates the best available evidence and the patient's individual needs.
2. This technique is particularly suited for clinical situations that are highly complex, in which important data are uncertain, patient input is critical, or events occur at different points in time.

3. The five steps of decision analysis are
   - Formulate the question.
   - Structure the decision and build a decision tree.
   - Fill in the data (probabilities and outcomes).
   - Determine the value of each competing strategy.
   - Perform sensitivity analyses.
4. A decision tree is composed of decision nodes (clinician or patient determines the path), chance nodes (uncertain path to be determined by chance), and terminal states (outcome health states).
5. Probabilities within the decision tree can derive from:
   - Clinical studies
   - Clinical databases
   - Expert opinion/calculated guesses
6. A utility is a quantitative measure of the strength of a patient's preference for a particular health state or outcome. Methods for assessing utilities include:
   - Visual analog scale
   - Time trade-off
   - Standard gamble
7. Solving the decision tree by averaging out and folding back will reveal the optimal strategy for the clinical situation.
8. Sensitivity analysis tests the stability of the results of the decision tree by systematically varying the values of particular probabilities and outcomes incorporated within the tree.
9. Discounting is a mathematical method for devaluing the future relative to the present. Complex clinical situations that assess prognosis or that evaluate multiple health states over time should be handled with a Markov model.
10. Although decision analysis may not be practical for every clinical situation, it can be a useful, logical, and evidence-based approach to medical decision making.

REFERENCES

1. Borrowed from Browner WS: Veterans Affairs Medical Center, San Francisco, California.
2. Weinstein MC, Fineberg HV: *Clinical Decision Analysis*. Saunders, 1980.
3. Sox Jr HC et al: *Medical Decision Making*. Butterworth Heinemann, 1988.
4. Pauker SG, Kassirer JP: Decision analysis. N Engl J Med 1987;316:250.
5. Jewell DP: Ulcerative colitis. Chapter 64 in: Sleisenger MH, Fordtran JS (editors): *Gastrointestinal Diseases*, 5th ed. Saunders, 1993.
6. Pemberton JH et al: Ileal pouch-anal anastomosis for chronic ulcerative colitis: Long-term results. Ann Surg 1987;206;504.
7. Fleshman JW et al: The ileal reservoir and ileoanal anastomosis procedure: Factors affecting technical and functional outcome. Dis Colon Rectum 1988;31:10.
8. Present DH et al: 6-Mercaptopurine in the management of inflammatory bowel disease: Short- and long-term toxicity. Ann Intern Med 1989;111:641.
9. Sandborn WJ: A review of immune modifier therapy for inflammatory bowel disease: Azathioprine, 6-mercaptopurine, cyclosporine, and methotrexate. Am J Gastroenterol 1996;91:423.
10. Provenzale D et al: Prophylactic colectomy or surveillance for chronic ulcerative colitis? A decision analysis. Gastroenterology 1995;109:1188.
11. Ekbom A et al: Ulcerative colitis and colorectal cancer: A population-based study. N Engl J Med 1990;323:1228.
12. Gyde SN et al: Colorectal cancer in ulcerative colitis: A cohort study of primary referrals from three centres. Gut 1988;29:206.
13. Lennard-Jones JE et al: Precancer and cancer in extensive ulcerative colitis: Findings among 401 patients over 22 years. Gut 1990;31:800.
14. Beck JR et al: A convenient approximation of life expectancy. Parts I and II. Am J Med 1982;73:883.
15. Read JL et al: Preferences for health outcomes: Comparison of assessment methods. Med Decis Making 1984;4:315.
16. Petitti DB: *Meta-analysis, Decision Analysis, and Cost-effectiveness Analysis: Methods for Quantitative Synthesis in Medicine*. Oxford University Press, 1994.

17. Chapman GB, Elstein AS: Valuing the future: Temporal discounting of health and money. Med Decis Making 1995;15:373.
18. Redelmeier DA et al: Probability judgment in medicine: Discounting unspecified possibilities. Med Decis Making 1995;15:227.
19. Johanneson M et al: A note on QALY's, time tradeoff, and discounting. Med Decis Making 1994;14:188.
20. Beck JR, Pauker SG: The Markov process in medical prognosis. Med Decis Making 1983;3:419.
21. Sonnenberg FA, Beck JR: Markov models in medical decision making: A practical guide. Med Decis Making 1993;13:322.
22. Weinstein MC et al: Forecasting coronary heart disease incidence, mortality, and cost: The coronary heart disease policy model. Am J Publ Health 1987;77:1417.