Weiss N. Clinical Epidemiology. The study of the outcome of illness. Oxford University Press, New York, 1986.

1 Clinical Epidemiology: What It Is and How It Is Used

Let's say that among your patients is a middle-aged man with intermittent claudication and that his symptoms have been increasing in severity over the last several years. His blood sugar level is normal, but he has a long history of cigarette smoking. The results of the physical examination are normal except for the absence of pulses in the legs. Should he be advised to undergo arteriographic evaluation and an operation for any surgically correctable lesions?

Among the questions that need to be addressed before making such a recommendation are the following: 1. What is the expected progression of symptoms and expected longevity in such a patient in the absence of surgical intervention? 2. To what extent is arteriography capable of (a) identifying remediable lesions, (b) not producing false-positive films, and (c) not producing adverse effects? 3. What is the likelihood (short- and long-term) that surgery can relieve symptoms or prevent progression while at the same time not cause complications? The area of research that attempts to provide answers to these sorts of questions is clinical epidemiology.

Epidemiology per se is the study of variation in the occurrence of disease, and of the reasons for that variation. It first entails making *observations* of individuals (or of populations), for instance, who develops disease and what are the characteristics of the ill or injured individuals that distinguish them from other persons. This process is followed by the formation of *inferences* as to which of these characteristics, or other unmeasured ones, played a role in causing the disease.

Clinical epidemiology is defined here in a parallel way: It is the

study of variation in the *outcome* of illness and of the reasons for that variation. The modus operandi is similar as well. First, observations are made as to the fate of ill persons—who recovers, worsens, develops complications, and what characterizes those who have different fates. Second, inferences are made as to the particular characteristics of the patient or his or her care that were responsible for these differences in outcome.

For many conditions, the most important determinants of outcome are diagnostic and therapeutic interventions. Because research in clinical epidemiology attempts to quantify the importance of these interventions relative to others possible or to none at all, the results obtained have direct applications for providers of health care.

To illustrate the questions that epidemiology and clinical epidemiology try to answer, let's return to our patient with claudication. Epidemiologic studies would make observations pertinent to the etiology of the symptom and its underlying pathology: Cigarette smokers and nonsmokers might be contrasted regarding the prevalence of claudication. If this study and others indicated a strong relationship, perhaps one that increased with the amount and recency of smoking, and if nonepidemiologic evidence were compatible with a deleterious effect of cigarette smoking on the peripheral arteries, then an inference of cause and effect could be drawn.

Clinical epidemiology, however, focuses on the consequences of the condition and the care given for it. Thus, observations might be made of untreated patients with claudication regarding the rate of change in symptoms, of other patients undergoing arteriography to determine the prevalence of surgically correctable lesions, and of still others who undergo surgery to assess the change in symptoms and/or physical signs. These studies would lead to inferences as to the role of surgery in achieving the intended purpose: To what extent was there improvement of symptoms and signs in patients who underwent these procedures? To what extent could any favorable outcomes be attributed to spontaneous regression of disease, or to selection for surgical therapy of patients destined to have favorable outcomes? If arteriography/surgery did produce improvements, what proportion of the patients undergoing arteriography was helped? By how much? Quantitative answers are necessary, for they will have to be balanced against the costs and hazards of arteriography and surgery (see below).

Though the term illness is part of the definition of clinical epidemiology, no attempt will be made to define it in any precise way. "Illness" is used here in a far broader sense than is "disease," which often refers to a particular set of anatomic or physiologic abnormalities. Illness may, for example, denote only a symptom that causes a patient to seek care, or to a physical sign detected by a provider of care. Since a large part of the utility of research in clinical epidemiology lies in its evaluation of the work of providers of health care, illness here will refer to any reason people have for seeking the services of such a provider. The methods of clinical epidemiology operate in the same fashion, whether they are applied to persons seeking care for health maintenance, for a specific symptom or sign, or for a disease.

WAYS IN WHICH CLINICAL EPIDEMIOLOGY IS PUT TO USE: DECISION MAKING

Virtually everything we can do for a patient has a "cost" attached to it. Costs can be measured in terms of labor and/or materials expended for the patient's care, such as those involved in taking a medical history, administering diagnostic roentgenography, or synthesizing and marketing a drug. A second cost relates to the deleterious effects on the patient's well-being of some aspects of the care provided. A barium enema will result in radiation exposure in all patients, cause temporary discomfort in most of them, and in rare instances lead to more serious consequences (e.g., bowel perforation). Digitalis will cause side effects in many patients, some minor (e.g., nausea) and some potentially severe (e.g., cardiac arrhythmias).

Ideally, no diagnostic or therapeutic measure should be undertaken unless its expected benefits to the patient exceed its expected costs. In most situations, an estimate of the relative magnitude of benefits and costs is easily made. In a patient with pneumococcal pneumonia, the therapeutic benefit of penicillin clearly outweighs the possibility of anaphylaxis (or other adverse effect) and the dollar cost of the drug. In an 85-year-old patient with angina, the various costs of coronary angiography and coronary artery bypass surgery almost always will outweigh the expected benefits in terms of symptom relief or (perhaps) increased longevity.

However, a number of situations confront the provider of care in which there appears to exist a near balance of benefits and costs.

For example, at present it is not clear to many providers whether, in order to detect cancer of the large bowel at an early stage, they should examine feces for occult blood using the Hemoccult test in asymptomatic, previously unscreened adult patients. In favor of the decision to use the test is the fact that some patients with undiagnosed cancer of this type who would have died of it will, instead, through treatment of tumors found at an early stage, be cured. Arguing against the use of the Hemoccult test in these patients is the cost of the test itself and the cost of evaluating further persons whose tests are positive but who do not have cancer.

In situations like this, one means of structuring the available information in order to guide the provider's use of diagnostic and therapeutic measures is *decision analysis.* The way in which decision analysis proceeds is illustrated in Figure 1-1. For purposes of this example it will be assumed that (a) the prevalence of cancer of the large bowel in this patient group is 2 per 1,000 and that, in the absence of Hemoccult testing, one-half of those with the cancer will die within the next 3 years; (b) 2% of those tested will be "positive," but among them 92% will be falsely positive (in most asymptomatic persons with blood in their stool, the source of the blood is not a malignancy of the large bowel); (c) a few people (0.04%) will test negative but will actually have the cancer; (d) the 3-year mortality in screened persons with cancer is only 40%, and that of persons without cancer is 2% (with or without screening); (e) other than cost, there are no negative attributes of Hemoccult testing (this will not necessarily be the case for other screening and diagnostic tests, the morbidity of which would have to be incorporated into the "decision tree").

The process of weighing the two alternatives (screen or not screen) begins by enumerating every possible category of patient, first of those who undergo testing and then of patients who do not. (For simplicity, the example described in Figure 1-1 ignores many important outcomes, primarily those relating to morbidity from colorectal cancer and its treatment.) Thus, the top "branch" in Figure 1-1 refers to patients who were screened, had a positive Hemoccult test, were found on further testing to have colorectal cancer, and who, despite the screening, died during the next 3 years.

Second, the proportion of patients in each category is estimated by multiplying together all of the probabilities of the "steps" that define the category. For example, the proportion of screened individuals found to be positive, who have colorectal cancer, and who

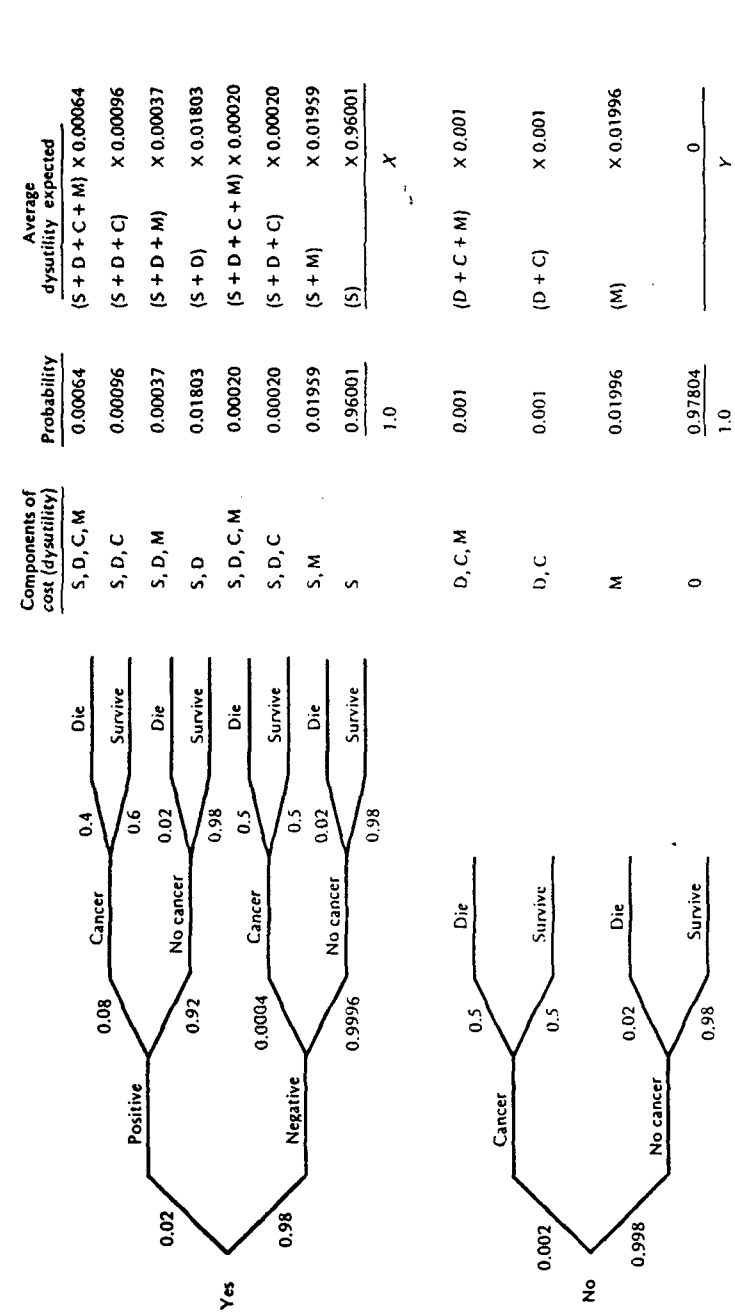


Figure 1-1. Decision tree for performing the Hemoccult test in asymptomatic patients.

die of the cancer within 3 years is equal to:

0.02	(proportion screened as positive)
× 0.08	(proportion of these patients who have cancer)
× 0.4	(proportion of cancer patients screened as positive
0.0064	who die within 3 years)

Third, a weight or value is assigned to each possible category. These values are the sums of the costs—monetary, physical, and emotional—of the disease and the testing and treatment of it. These values are all negative, for the occurrence of cancer of the large bowel exerts a negative influence on the population's health; hence the terms costs and dysutilities used in Figure 1-1 and hereafter. In question is whether or not the expenditure of some of the population's resources, for instance, on screening, will diminish this negative influence.

Fourth, the proportion of patients in each category is multiplied by the negative value attached to that category. Finally, the sum of these products ("average dysutility expected") for persons undergoing Hemoccult testing (X) is compared with the corresponding sum for persons not tested (Y). If $X < Y$, then testing should be recommended.

Often there is uncertainty as to the probability with which some of the events occur, for instance, the probability of death among screened and unscreened persons with colorectal cancer, or as to the size of the dysutility associated with a particular category of patient (see below). A useful feature of decision analysis is that, once the structures of the decision trees have been developed, the extent to which the decision is affected by changes in the probabilities of the various outcomes or in the particular set of dysutilities chosen can be determined. This process of determining if the decision is influenced by changes in the input information is called "sensitivity analysis." It allows the decision-maker to determine how solid his or her choice is, despite imprecise knowledge.

This book is devoted to describing the means by which one measures the probability of occurrence of the steps that define each category of patient outcome, but as for the measurement of the dysutilities, a few paragraphs here must do. Certainly, some of the dysutilities are easy to estimate accurately, for example, the dollar cost of the Hemoccult test and of the procedures needed to secure a diagnosis. The impact of having the cancer is harder to quantify. The average cost of treatment can be determined, but what of the physical and psychological effects? And what is the "cost" of death? And, if we are to complete the decision analysis, how can we put these dollar, illness, and death dysutilities in the same units?

As difficult as the task is, in order for providers to make rational decisions regarding the delivery of health care—whether or not they employ decision analysis in a formal way—it is necessary that they weigh the various negative events on a common scale. Most often, the scale is a monetary one. The idea of assigning a certain monetary value to health or to a human life is an unappealing one to most of us, and rarely is anyone in a position to knowingly cause loss of health or life in a specific individual by failing to make a dollar expenditure. Nonetheless, society chooses to allocate only so many of its dollars for reducing the probability of illness and death among its members. We are willing to pay so much, but not more, for road safety, for example. It is probable that additional highway dividers or railroad bridges would prevent some injuries and an occasional accidental traffic death, but in many instances we are unable to "afford" them. Or, perhaps, we may believe that installation of a highly trained, rapid-response, emergency medical service in a town of 10,000 persons could lead to the survival of one person who develops cardiac arrest each year, but it is likely that in many towns of this size, the expense of operating such a program is beyond what the populace is willing to pay.

Since society is responsible for the overwhelming majority of expenditures for health care, the wishes of society should play the major role in determining whether or not individual health care expenses are met as well. Though a provider of health care is committed to doing everything possible to promote a patient's health, the range of what is possible should be delineated by those who will pay the bill. Thus, there are instances in which a health care provider, conscious of society's needs, actually will make recommendations or take actions that fall short of those that he or she would implement if resources for health care were unlimited. Such a provider realizes that these resources *are* limited—what is consumed for one purpose is not available for others. The goal of the health care provider, then, is to use these finite resources in the most efficient way. For example, a provider might be willing to do a Pap smear every 3 years rather than more frequently in women already screened several times as negative, not because this approach is adequate to prevent all mortality from cervical cancer in such patients but because it is a reasonably inexpensive way to prevent *most* of it.

Example. In patients with acute chest pain, several clinical characteristics have been identified that are correlated with the presence of myocardial infarction. A group of investigators (Fineberg et al., 1984) attempted to assess the economic and health implications of two types of acute care in patients with chest pain who are in a "low" risk group (probability of myocardial infarction less than 1 in 20): (a) admission to a coronary care unit versus (b) admission to an "intermediate" care unit (i.e., one that would permit electrocardiographic monitoring and the administration of prophylactic lidocaine but not intensive nursing care). They estimated that there would be a small excess of deaths from ventricular fibrillation and complete heart block in the group placed in intermediate care. Nonetheless, they concluded that "patients who have a low risk for myocardial infarction would be appropriate candidates for admission to an 'intermediate' care unit, since the provision of the facilities of a coronary care unit to all low risk patients would cost an estimated additional $2 million per life saved."

If we are (reluctantly) willing to assign costs to the loss of health and human life, how do we go about deciding what these costs should be? To catalog the techniques that have been devised to do this is beyond the scope of this book, so an example will suffice: One could visit a sample of residents in the hypothetical town mentioned earlier, describe the emergency medical service and its expected benefits (in terms of lives saved), and ask how much each resident would be willing to add to the annual town tax to enable such a service to be established. The average dollar figure obtained in the sample, multiplied by the number of persons in the town, divided by the number of lives saved per year (1.0 in this example) gives an estimate of how much the townspeople would be willing to spend in the effort to prevent the loss of one life.

This and other methods of estimating the "cost" of a human life clearly are not going to be as precise as those that estimate screening costs, hospitalization costs, and so on. For this reason, it is particularly important to determine how sensitive any decision is to changes over a plausibly wide range of such costs.

It is possible to further embellish this process by incorporating the fact that, when forced to make the choice, most of us would save the life of (a) a 30-year-old rather than an 80-year-old, or (b) someone with no disability rather than a quadriplegic. What emerges from this refinement is a comparison not of dollars per life saved but rather of dollars per ***quality-adjusted years*** of life saved. Embellished or not, the basic idea is that in making decisions about expenditures that could prevent mortality or morbidity—whether such decisions relate to highway design, emergency medical services, or clinical practice—the question of the cost of that prevention is always considered, at least implicitly.

In summary, the process of decision analysis requires two ingredients: the "cost" associated with each category of patient outcome, either a direct dollar expenditure or a physical manifestation (illness, death) that is translated into a monetary equivalent, and the likelihood of each outcome. Estimating the latter is the business of clinical epidemiology, and it involves estimating first the probabilities at each "branch" of the decision tree. These then are multiplied together to arrive at an estimate of the overall likelihood. So, in attempting to determine if it is desirable to perform testing for fecal occult blood (Figure 1-1) it is necessary to estimate the probability of (a) test positivity, (b) positively and negatively testing persons having cancer of the large bowel, and (c) the survival of persons with cancer conditional on being tested and (if so) on the test results. Clinical epidemiologic studies are those that gather data from which these probabilities can be assessed. The resulting probabilities then can be used to make inferences regarding (a) the usefulness of a diagnostic or screening test, (b) the efficacy or safety of a therapeutic measure, and (c) the likelihood or speed with which progression or complications occur in persons with a given condition ("natural history"). These topics are dealt with, in turn, in the rest of this book.

QUESTIONS, CHAPTER 1

1-1. You are the head of a general surgical unit. For patients who have undergone cholecystectomy, the unit's policy has been to require a minimum of 10 postoperative days of hospitalization. However, you are aware that others have developed a policy of hospital discharge as soon as a patient meets a number of preset clinical criteria (e.g., no requirement for parenteral analgesics or nursing care for eating and dressing, return of urinary and bowel function, good wound healing), irrespective of duration of postoperative stay. You mention the issue to your hospital administrator, who encourages you to look further into this potential cost-saving approach.

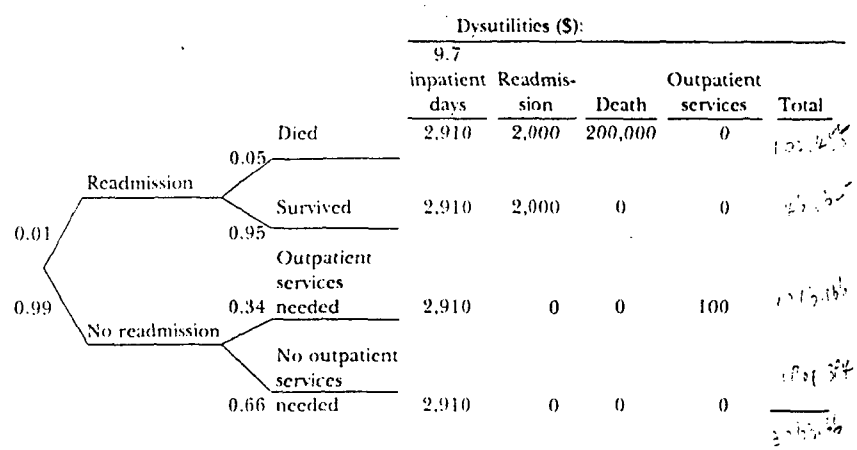
You come upon in the literature a report of a randomized controlled trial that has tested these two postoperative strategies ("fixed" vs. flexible" stay) in 100 patients (Simpson et al., 1977). The results are summarized below:

	Patient group: "Fixed" post-op stay (n = 47)	"Flexible" post-op stay (n = 53)
Mean duration of post-op stay (days)	9.7	7.6
No. of hospital readmissions	0	0
No. of post-op deaths	0	0
No. with need for outpatient services within 3 weeks of surgery	16 (34%)	29 (55%)

While the policy of flexible discharge based on fulfillment of clinical criteria led to a 2-day reduction in length of hospital stay, it also led to an increase in utilization of outpatient services. In addition, it is possible that the frequency of hospital readmission (and possibly of late postoperative mortality) might be increased in the flexible discharge group, but that in a study of only 100 patients such an increase might not have been detectable.

To sort out these issues in a systematic way, you perform an elementary decision analysis. For the fixed-stay group, you construct the following decision tree:

"Fixed" post-op stay



In setting up the tree you make a guess that some of these patients (say, 1%) will require readmission, and that 5% of those readmitted will die as a complication of surgery. (For simplicity, you assume that no one requiring readmission will also require outpatient services and that no one who is not readmitted will die of these complications.) Your administrator tells you that 1 postoperative day in the hospital costs about $300, and you estimate a readmission to last 5 days at $400 per day. From the literature you find an estimated "value" for a human life that is on the high side ($200,000) and guess that outpatient costs would be around $100.

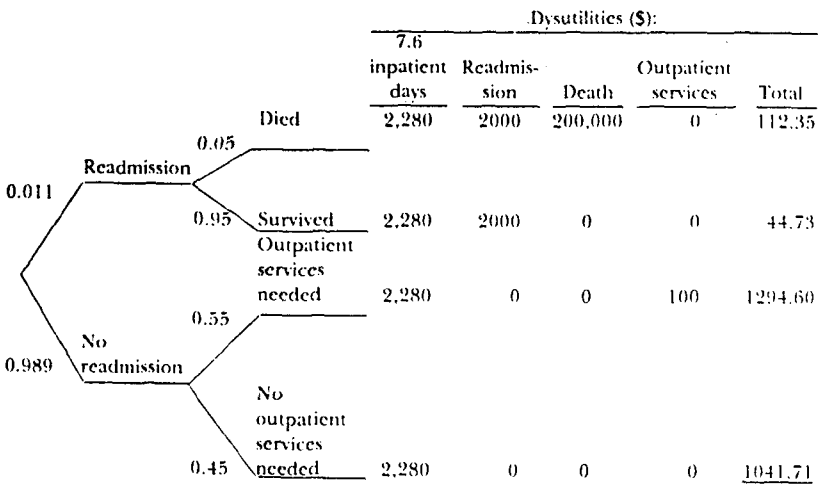
What is the total average postoperative cost associated with this fixed-stay policy?

1-2. Construct a similar decision tree for a flexible-stay policy. Calculate the total average postoperative cost associated with this policy, assuming that the possibility of readmission is higher than that under the fixed-stay policy by a factor of (a) 1.1, (b) 2, or (c) 5. (Assume that among those readmitted, the probability of death remains the same as under the fixed-stay policy, i.e., 5%.) Based on this analysis, which of the two policies should you adopt?

ANSWERS

1-1. $3,063.66

1-2. *"Flexible" post-op stay*



Probability of readmission	Average post-op cost of flexible-stay policy
0.011	$2,466.40
0.020	$2,573.90
0.050	$2,932.25

Even under the extreme assumption of a fivefold increase in the occurrence of complications leading to readmission and death, the average postoperative cost per case under the flexible-stay policy is less than that ($3,063.66) under the fixed-stay policy. Thus, based on the factors considered here, it would be prudent to switch to the flexible-stay policy for patients recovering from cholecystectomy.

REFERENCES

Fineberg HV, Scadden D, Goldman L: Care of patients with a low probability of acute myocardial infarction: Cost effectiveness of alternatives to coronary-care-unit admission. *N Engl J Med* 1984; 310:1301–1307.

Simpson JEP, Cox AG, Meade TW, et al: "Right" stay in hospital after surgery: Randomised controlled trial. *Br Med J* 1977; 1:1514–1516.