

# INTRODUCTION TO COST-EFFECTIVENESS

## Overview

Imagine that you are the director of a large cancer society. Your day-to-day duties require you to conduct some research and oversee employees whose job is to compile data and make health recommendations. One morning you sit down with a cup of coffee and toast, and when you open the morning paper you find that one of your society's recommendations—that women between the ages of 40 and 60 receive screening mammography for breast cancer—has made the headline news. An elderly-rights group is suing your society. This group argues that your recommendation unfairly discriminates against the elderly because you have implied that women over the age of 60 should not be screened for breast cancer.

You rush to the office and find that the teams who made the recommendation are already in a heated meeting. They have split into two factions, and each group is now accusing the other of making bad decisions. But did they? You manage to calm everyone down and review the process they used to arrive at their recommendation. You learn that both groups were concerned that recommending mammograms for women over a wider age range might become very costly, thereby jeopardizing screening for women who might benefit from screening mammography the most.

One group argued that it made sense to screen older rather than younger women. Mammography works better in older women, who have less dense breast tissue. Older women, they reasoned, were less likely to have a falsely positive mammogram and therefore would be less likely to suffer unnecessary procedures or surgery.

## LEARNING OBJECTIVES

- Explain why cost-effectiveness is useful.
- List the elements of a cost-effectiveness analysis.
- Distinguish between an average cost-effectiveness ratio and an incremental cost-effectiveness ratio.
- Explain the difference between efficacy and effectiveness.
- Describe how cost-effectiveness analysis influences policy.

Unnecessary interventions, they noted, place women at risk for surgical complications, are psychologically traumatic, are costly, and may do more harm than good.

The other group argued that it was unwise to actively screen all elderly women with mammography, because women who had breast cancer would die from other natural causes before the cancer had a chance to spread. After all, breast cancer can take more than a decade to kill, and the life expectancy of older people is limited. Therefore, they reasoned, elderly women would be subjected to an uncomfortable and expensive screening test that would have little impact on the length of their lives. Besides, who would want to undergo chemotherapy in the precious remaining years of their lives?

Both factions made arguments based on sound scientific, economic, and social research, but which group's approach would be best for patients? You and your employees decide to conduct a more extensive analysis of the costs and benefits of breast cancer screening and plan to send out a press release to this effect. But where do you start?

You might start by having a team estimate the likelihood that older women will die of breast cancer if they are not screened and have another team estimate the number of women who are likely to have false-positive mammograms at different ages. You might also wish to obtain information on the number of years of life that mammography will save, the quality of life for women who have different stages of breast cancer, and the psychological impact of a positive test result among women who do not in fact have breast cancer (**false-positive test results**). Because both teams were concerned about the costs of mammography, you may also wish to calculate the cost of screening mammography and the cost of all of the medical care that might be averted by detecting breast cancer at an early stage. Finally, because each team is interested in knowing whether women in both age groups might benefit from mammography, you decide that the costs and health benefits of screening each group should be compared to not screening women at all. If all of these factors were put together in a systematic manner, you would have conducted a cost-effectiveness analysis.

## Why Cost-Effectiveness Is Useful

Now let's take a step back and consider why all of this is important in the first place. Certainly you want to know whether mammography is going to lead to net improvements or net declines in health relative to some standard of care. If it's only going to hurt people, we certainly don't want to do it. But if we know it helps, we also want to know whether it is affordable.

What does "affordable" mean when you are talking about human life? Take a moment to imagine what we could do with an infinite amount of

money. We could build a huge public transportation system that eliminates car accidents, pollution, and noise. We could use only solar power and switch to 100 percent recycling, eliminating the major remaining sources of pollution; this would greatly reduce environmental carcinogens and oxidizing agents that cause cancer, heart disease, and premature aging. We could completely mechanize industry, eliminating occupational accidents. Finally, we could create a highly advanced health system that provides full MRI body scans and comprehensive laboratory screening tests for everyone in the population to ensure that cancers and other disorders are detected at the earliest possible stage.

As it is, there are very few nations that can even provide safe drinking water to all their citizens. The challenge, then, is to figure out how best to spend the money we have so that the quantity and quality of life can be maximized.

Thus, even if mammography screening for breast cancer is on the whole effective, it is conceivable that the money spent on it could save more lives if it went toward something else. **Cost-effectiveness analysis (CEA)** helps determine how to maximize the quality and quantity of life in a particular society that is constrained by a particular budget.

We'll get deeper into this later in the book, but let's examine the specifics of the example to illustrate how resource allocation might work. Assume that the U.S. Congress decided to allocate \$1 trillion to the competing health projects we mentioned. It could choose public transportation, greatly reducing pollution (a cause of pneumonia, cancer, and heart disease) and motor vehicle accidents (the fifth leading cause of death). It could invest in clean energy, reducing dependence on oil while reducing air pollution. Or it could choose the universal MRI strategy, detecting more tumor-producing cancers, some of which can be cured if detected early. If Congress knew the cost per year of life saved, it would know how to maximize the number of lives saved with the \$1 trillion investment.

One thing that might strike some readers as a bit strange about this hypothetical situation is that we are essentially deciding who lives and who dies. If we save the mothers and fathers with cancerous tumors by opting for universal MRI examinations, many sons and daughters will die in car accidents as a result. Behind these numbers are real people affected by whatever decision is ultimately made. The more tangible these lives are made to the decision makers, the more difficult the decision becomes.

As one physician, Paul Farmer, points out, you cannot let a person die in front of you when you know that an effective treatment exists (Farmer, 2004). Is the solution, therefore, to start a medical clinic, even if it comes at the expense of a more effective vaccination campaign? We might know that one intervention saves more lives than the other. However, when

the most cost-effective intervention saves lives we will never see—lives that lie abstracted in numbers—it is more difficult to rationalize the choice.

Nevertheless, policymakers must often make abstracted decisions based on data from cost-effectiveness analysis, and these sometimes involve decisions that improve survival for one group at the cost of survival for another. (We'll see an actual example of this later in the book.) These decisions become more abstract when quality-of-life issues are added to the mix of life-and-death issues.

The sad reality is that making decisions based on “gut feelings” leads to more suffering and more death than making decisions based on science. While the US tends to operate on “gut policy,” other rich nations use science to allocate scarce resources. This may partly explain why health and longevity are declining in the US but are increasing in other rich nations.

## Elements of Cost-Effectiveness Analysis

Just as a driver really only needs to know about the accelerator, brake, and gearshift before driving a car for the first time, this section provides the basic parts of a cost-effectiveness analysis that you need to have in your head before you can start getting down to business. As we get further into the book, you'll be introduced to more advanced and complex methods that will build on the foundations of earlier chapters.

## Health Interventions

A **health intervention** is a treatment, screening test, or primary prevention technique (for example, vaccinating children to prevent measles). Health interventions typically reduce the incidence rate of disease or its complications, improve the quality of life lived with disease, or improve life expectancy. Most produce some combination of these benefits. The benefits of a health intervention are referred to as **outcomes**. Health outcomes can assume any form, but the most common health outcomes are big-picture items, such as hospitalizations prevented, illnesses avoided, or deaths averted (as opposed to little-picture items, such as stomachaches reduced).

The first question that should pop into mind when speaking of the cost-effectiveness of a particular intervention, such as mammography, aimed at improving a health outcome, is “Relative to what?” Mammography will certainly appear cost-effective if we compare it to a total body scan for breast cancer. But it might not be cost-effective relative to educating women to perform breast self-examinations in the shower on a regular basis. The intervention to which you are comparing the intervention of interest is called the **competing alternative**.

## The Competing Alternative

Improvements in health states and improvements in length of life do not always go hand in hand. For instance, we perform mammography even though the procedure produces discomfort. Likewise, we provide steroids to patients with asthma even though this medication can be harmful over the long term. Such complications shouldn't be a deterrent. The whole point of cost-effectiveness, after all, is to examine the optimal course of action when there is considerable uncertainty. (Otherwise, why bother with the analysis in the first place?)

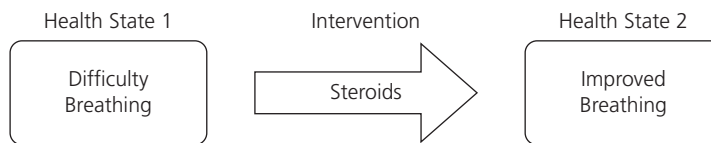
Virtually all health interventions cost something up front. But they also affect the amount of money spent on future medical care. For instance, a woman who is found to have breast cancer at an early stage will likely incur the cost of hospitalization and surgery in addition to the mammography, but the cancer may be cured, averting the future cost of more severe disease. Thus, mammography can produce value by averting disease and future costs. In short, the overall cost and overall effectiveness of any given alternative strategy are not often apparent on first glance.

So what is the net (overall) cost of mammography, and how much benefit can we expect? To answer this question, we first want a sense of how much of an improvement in health states we'll get from mammography over the long term.

## Health States

While health outcomes such as deaths are concrete overarching measures of health, it is also important to examine more specific improvements in one's state of health, such as reduced pain or improved ability to walk. Specific states of health are quite logically referred to as **health states**. (Whoever said cost-effectiveness was difficult?)

Figure 1.1 shows how a health intervention improves health states. Here, we see that people having an asthma attack arrive at the emergency room with difficulty breathing (Health State 1). The health intervention is to provide intravenous steroids and aerosolized medications to help such



**Figure 1.1** Example of the Effect of a Health Intervention on the Health States of Patients Admitted to the Emergency Room for an Acute Asthma Attack

patients breathe. Typically, patients experience dramatic improvements in breathing once treated (Health State 2).

Simple. So why the fuss? We wish to first think about this in very simplistic terms because we will later need to think about the various ways in which health states change when a medical intervention occurs, which can be somewhat complex. Collectively, changes in health states add up to changes in one's **health status**.

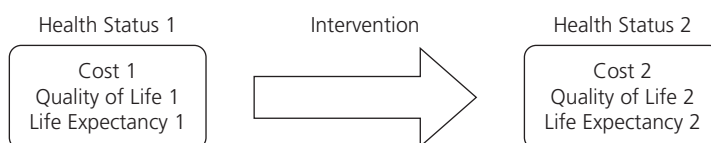
## Health Status

A person's health status is the sum of his or her health states. Changes in health states are associated with an intervention are not always positive. Steroids can lead to an improved health state, but, over the long-term, can negatively impact health status. Conversely, mammography will often lead to a decline health states over the short-term in the hope of garnering long-term benefits. The vast majority of patients told that they might have breast cancer actually have a false positive test result, leading to psychological distress. If someone can jog and isn't anxious or depressed, we might say that the person has an excellent health status based on those two health states alone.

In a cost-effectiveness analysis, a researcher gathers information on the ways in which a health intervention changes the average health status of a group of people alongside costs (Figure 1.2). Imagine for a moment you are evaluating a treatment for bacterial pneumonia and comparing it to no treatment at all. In Figure 1.2, Health Status 1 represents the collective health states of untreated people, and Health Status 2 represents the collective health states of treated people.

Suppose we're looking at treatment of bacterial pneumonia with antibiotics. Someone with bacterial pneumonia might have pain with breathing and a fever and be confined to bed. Someone who has been treated would have less pain and less fever and might be able to get around. In other words, the treated person would experience an improvement in health status.

Because health status is an amorphous concept, there is no direct way to measure it. Instead, cost-effectiveness analysis examines the quantity of life (mortality) alongside a measure of the quality of life (morbidity)



**Figure 1.2** Components of a Cost-Effectiveness Analysis

associated with a given health status. The point of a cost-effectiveness analysis is therefore to estimate what an improvement in health status will produce in terms of quality and quantity of life and how much it will cost to achieve these improvements.

We must also look at how health status (the collection of health states) changes over time. For instance, suppose you are again at your job at a major cancer society, and you are trying to decide whether to recommend screening mammography. Cancer evolves over many years. So we'll want to know how it will affect everything from a patient's ability to perform daily activities to her mental health as time goes on.

Take another look at Figure 1.2. The quality of life in Health Status 1 for women screened for breast cancer is higher over the short term than it is in Health Status 2. Women in Health Status 1 have not undergone the pain of having their breast squeezed between two metal plates and do not have to face the pain and suffering associated with the diagnosis (or a misdiagnosis) of breast cancer if it is detected. In fact, since the cancer is producing no symptoms and the women do not know that they have breast cancer, they will be as subjectively healthy as anyone else over the short term. But the women in Health Status 2 (undetected cancer) may not have to face the pain and suffering associated with advanced breast cancer in the future.

Finally, the length of life is shorter for women who have not received a mammogram (Life Expectancy 1) than for those who have (Life Expectancy 2). This is a critical factor that must be considered in any cost-effectiveness analysis. But what do we do with all this information on health status and life expectancy? Enter the **quality-adjusted life-year (QALY)**.

## The Quality-Adjusted Life-Year

Consider the nuanced changes in the quality of life that occur when a person with diabetes is given a medication to lower blood sugar. At first, the patient has to take a pill and may think of herself as sicker than she did before being given the prescription. But over time, this pill might prevent a myocardial infarction, which would have a grave impact on the person's perception of her health and her ability to get around or to do other things she enjoys. In other words, it affects many different dimensions of this person's health, or many different health states. Together, real-world improvements in these health states, along with their effect on life expectancy that occurs when a health intervention is applied, constitute the effectiveness of that intervention.

Just to drill the point home, a health outcome (such as a myocardial infarction) leads to changes in one's health states (ability to walk, work, or

even to have sex), which in turn affect the person's quantity and quality of life. If we could somehow combine a measure of quantity of life adjusted for the quality of life, we would be just about set in terms of measuring the effectiveness of any given health intervention.

As it turns out, we have just such a thing: the quality-adjusted life-year, which is more affectionately known as a QALY. The QALY is a year of life lived in perfect health. How does the QALY work? Imagine that your last year of life wasn't such a great one. Your spouse left you alone and took your beloved dog. You became depressed. There were times when you were just fine and times when you wanted to die, but on average you felt like it was worth a lot less than other years you have had. There is a magic fraction that is used to account for the total value of the life that was worth living over that year. We will get into how this (questionably) magic number is calculated later, but for now assume that it is 0.5. You are otherwise in outstanding health, but the depression made the year only worth the equivalent of half the prior years in which you were both in good physical and mental health. Even though you lived a full year, it was just one-half a year ( $0.5 \times 1$  year) of perfect health.

At any given age, the average number of years we can expect to live is our life expectancy. Therefore, the average number of QALYs we can expect to live is our **quality-adjusted life expectancy (QALE)**. For example, as with a single QALY, if a person is expected to live for 10 years with a quality of life that is reduced by one-half due to a disease, then her total QALE is 5. QALE is the average number of years one can expect to live adjusted for quality of life for those expected lived years. Throughout this book, you'll become increasingly familiar with what a QALY is, how it is calculated, and how it is used. In addition to the QALY, measurements of benefits and efficacy can also include life-years (LYs) and disability-adjusted life-years (DALYs). We will discuss this in more detail in Chapter 8. For now, just accept that a QALY is a year lived in perfect health.

## Costs

For a moment, let's consider the changes in costs associated with mammography. The total cost of mammography includes those costs associated with the mammogram as well as future medical costs incurred as a result of this screening test. These future costs will include the value of lost work and the medical costs associated with treating cancer that was detected early.

Failing to provide a screening test also costs something. These costs include those associated with treating breast cancer that is so advanced



that it is self-evident to the patient or is easily detectable on physical examination. People with advanced breast cancer will incur higher medical costs and miss more work than will those who were diagnosed early in the course of illness. All of these costs must ultimately be considered.

When comparing mammography to no mammography, the difference in costs, morbidity, and mortality is captured in the *incremental cost-effectiveness ratio*. This tells you how much you will need to spend to realize a unit gain in effectiveness.

## The Average and Incremental Cost-Effectiveness Ratio

Ratios put medical information into perspective. For instance, if a physician knows that there are 180,000 new cases of breast cancer a year in the United States, she will not be able to provide much information to a woman worried about developing that disease. If the physician knows that there are 11 new cases per 10,000 women each year, she will have a much better idea of how to communicate the risk. Similarly, the average cost-effectiveness ratio provides the consumers of our research with information that describes the average cost-per-treatment effect for a given strategy. In most cases, this will be the average cost per QALY.

The average cost-effectiveness ratio is the net cost of an intervention divided by its net benefit gain versus the no-intervention option. When the net costs and benefits are compared to *another* competing strategy, we end up calculating the **incremental cost-effectiveness ratio (ICER)**. So, instead of just calculating the average cost and QALYs among women who receive breast mammography relative to no mammography, the ICER provides the relative difference in cost associated with one strategy (say self-screening) versus the difference in effectiveness of the competing alternative. In other words, it tells you how much you will spend to buy additional QALY (benefits) relative to the competing alternative.

Let's take an example other than mammography to give you a break from that topic. Suppose you are working for a pharmaceutical company that just came out with a powerful new antibiotic for treating staphylococcus infection, Staphbegone. It is more effective than other antibiotics at saving life, but it's also much more expensive than what is now being used, Staphbeilln. But it will also get people out of the hospital faster, so it will reduce hospitalization costs and produce improvements in health-related quality of life.

We want to compare Staphbegone to Staphbeilln. We put Staphbeilln on the right-hand side of the equation because it is less effective (this ensures

that the ratio will be positive if the intervention costs money but improves health and negative if the intervention saves money and improves health). If we call the old drug “intervention 1” and the new drug “intervention 2,” the ICER takes the form:

$$\frac{(\text{Cost of intervention 2} - \text{Cost of intervention 1})}{(\text{QALE 2} - \text{QALE 1})} \quad (1.1)$$

Recall that QALE refers to quality-adjusted life expectancy, or your remaining life expectancy in perfect health.

Here, quality-adjusted life expectancy is used in the denominator because this is the standard unit of effectiveness (more on standardization in Chapter 2). However, in some cases (also discussed in Chapter 2), other measures of effectiveness might be used. We interpret the ICER as the additional costs invested in one strategy versus a competing strategy for an additional gain in benefit (e.g., QALY). In other words, we would have to invest in some cost for Staphbegone to receive a benefit equivalent to one additional QALE gained relative to Staphbeilln. Depending on our budget constraint, Staphbegone may be considered cost-effective relative to Staphbeilln.

Now you should have a general idea of what cost-effectiveness is. You should also have an idea of what the incremental cost-effectiveness ratio means. In the next section, we move from what cost-effectiveness is to why cost-effectiveness analysis is a critical part of any well-functioning society.

### *Exercises 1 and 2*

- Suppose that a complete course of Staphbegone costs \$12,000 and a complete course of Staphbeilln costs \$4,000. The average hospitalization costs \$1,000 per day. Patients given Staphbegone have an average length of hospitalization of 5 days and Staphbeilln have an average hospitalization of 10 days. What is the incremental cost of Staphbegone?
- Persons given Staphbegone have a higher survival rate than those given Staphbeilln. On average, those given Staphbegone can expect to go on to have a quality-adjusted life expectancy of 35 QALYs, while those given Staphbeilln go on to live 34.5 QALYs. Using the answer from Exercise 1, what is the incremental cost-effectiveness of Staphbegone?

#### **TIPS AND TRICKS**

Answers to all self-study questions are presented in Appendix A.

## Why Conduct Cost-Effectiveness Analysis?

There are a number of ways to prevent or treat most diseases. For instance, breast cancer can be detected by self-examination, examination by a medical practitioner, screening mammography, ultrasound, spiral computed tomography (CT), or magnetic resonance imagery (MRI). It is also possible to compare different levels of intensity of a single health intervention. For example, screening mammography might be performed every six months, every year, or every two years. Each of these competing alternatives is associated with a different effectiveness and a different cost (Mandelblatt et al., 2004). In the real world, many different approaches are used to diagnose or treat disease (Krumholz, 2013; Newhouse & Garber, 2013; Wennberg & Gittelsohn, 1982), some by crackpot medical practitioners.

Many students of cost-effectiveness analysis rightly question the logic of choosing interventions based on both cost and effectiveness criteria rather than effectiveness alone. It seems to many people that we should purchase the most effective screening or treatment procedure irrespective of its cost. In the first section of this chapter, we saw that there is an almost infinite number of lifesaving expenditures, including some combination of screening modalities. The question, then, is “Which ones can we afford?” To answer this question, let’s first consider what we mean by *cost* and what we mean by *effectiveness*.

### Costs Matter

Even when the most effective modality is known, it may have unforeseen effects on health and longevity if its use takes vital resources from other social programs. First, consider your personal budget. Suppose that you make \$2,000 a month. Now suppose that your rent, minimum food purchases, basic utilities, and transportation come to \$1,800. You could spend some of the \$200 on going out to the movies and save the rest. Alternatively, you could live it up and go out to a fancy dinner and the theater five nights a month and live without electricity, go on an expensive vacation and not pay your rent, or blow the whole wad on that haute couture suit you’ve always wanted. Some of us can accept that it’s not possible to consume everything we want. But when the goods and services we are consuming define who lives and who dies, the choices become much more difficult.

Consider the case of a tiny country with 100 people and a total health budget of \$10,000 per year. If the country paid for expensive organ transplants, it could spend its entire budget on one person, leaving nothing for clean water, vaccinations, primary care, or other medical services that greatly prolong the quality and quantity of life for everyone in the country. If it instead spent \$1,000 per year to keep vaccinations up to date, \$7,000

per year for all needed antibiotics and basic primary care, and \$2,000 per year on emergency surgery, many more lives would be saved. The value of goods and services in their best alternative use is the **opportunity cost** of an investment, such as a medical intervention.

Thus, just as your electricity bill has an opportunity cost, so does vaccination.

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## THE CASE FOR EDUCATION AS A HEALTH EXPENDITURE

Basic schooling is thought to greatly reduce morbidity and mortality in both the industrialized and the developing context. Education provides the cognitive skills and the social credentials needed for survival and adaptation to any ecological niche (Wilkinson, 1999). For instance, middle-class neighborhoods tend to have lower rates of crime victimization, access to healthier foods, and better housing. None of this is likely possible without an adequate education. Similarly, cognitive skills allow people to better assess hazards (such as taking the train instead of a bus in India) and may even reduce errors in medication dosage or compliance with medical prescriptions. As it turns out, education not only saves lives; it saves money (Muennig, 2015; Muennig & Woolf, 2007). Therefore, it can be argued that basic education should be prioritized over the provision of basic medical services when resources are slim (Muennig & Woolf, 2007).

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In circumstances where health funds are limited, cost-effectiveness analysis can provide information on how to realize the largest health gains with the money that you have (Gold, Siegel, Russell, & Weinstein, 1996; Neumann, Sanders, Russell, Siegel, & Ganiats, 2016; Ubel, DeKay, Baron, & Asch, 1996). For instance, in a country with a national health system, interventions can be ranked in order of their cost-effectiveness. If we know how much will be spent on each health intervention, it becomes possible to go down the list until the money runs out. This is also known as **appropriate technology utilization**; if a government barely has money to pay for vaccination (an appropriate technology), it does not make sense to pay for heart-lung transplants (a technology that is inappropriate given the budgetary constraints).

The use of appropriate technology isn't always popular. A person who needs a heart and lung transplant and is dying in the hospital evokes more sympathy than the unseen hundreds of people who might benefit from all of the vaccines that could be purchased with the same sum of cash. However, in the absence of sufficient funding to cover all known treatments for all known diseases, prioritizing expensive and less effective interventions will ultimately lead to more illness and death.

In the United States, medical care is almost never denied to anyone who can afford it, and there is no absolute cap on how much is spent on health care. In this setting, cost-effectiveness analysis can provide clinicians, policymakers, and insurers with general guidelines on which interventions might generally be preferable. For instance, an intervention that costs \$100,000 for each QALY it produces relative to the next most effective alternative might be seen as expensive by some but might be purchased by others.

While highly anecdotal, this lack of an emphasis on cost-effectiveness likely provides a partial explanation for why the United States spends the most on health care as a proportion of gross domestic product but ranks about fifty-third among nations worldwide in terms of life expectancy in 2015. To get the latest data, you can search for “life expectancy rank of all nations” on the Wolfram|Alpha web site (Wolfram|Alpha, 2015). You will almost certainly note that it the US has fallen even more by the time you read this.

In developing nations, where government health budgets may be as low as \$5 per person, the need for cost-effectiveness analysis becomes critical (Attaran & Sachs, 2001). In the African continent, per capita government health-related expenditures ranged from US\$2 to US\$612, and 56 percent of nations had a per capita government health-related expenditure of US\$20 (Sambo, Kirigia, & Orem, 2013). When budgets are small, the use of inappropriate technologies can greatly increase mortality in the population as a whole. Why more so than in industrialized nations? Simply because forgoing the least expensive and most effective interventions such as vaccinations produces more harm than forgoing interventions that produce less spectacular gains and cost more, such as dialysis. The basis for such decisions, therefore, has at least as much to do with its effectiveness at a population level as its cost.

## Effectiveness Versus Efficacy

Usually tests, treatments, or interventions are measured in terms of their **efficacy**. Efficacy reveals how a test, treatment, or intervention works under experimental conditions. Experiments tend to work better under the watchful eye of researchers in a controlled laboratory setting than in the real world. Subjects are watched to make sure they take their medications and that laboratory specimens are properly frozen and shipped immediately for testing. In the real world, conditions tend to be less ideal.

Experiments that measure efficacy also tend to look at only short-term outcomes. There is often one best test, treatment, or public health

intervention with respect to short-term efficacy. But can we say that the use of the most efficacious interventions will detect the most cases of disease, have the highest rate of treatment success, or prevent the most diseases in the real world?

Sometimes, the answer is no. Not only are tests performed differently or medications taken in different doses in the real world relative to within precise scientific experiments, but a number of other unexpected things happen as well. For instance, screening tests and treatments are sometimes associated with hidden dangers. As we saw in the screening mammography example, a false-positive mammogram can lead to unnecessary surgery and psychological stress. If the woman is unlikely to have breast cancer, we have to ask whether the risks outweigh the benefits. Many societies promote testing for diseases for which there is no cure and early cancer detection does nothing. Screening for pancreatic cancer can be accomplished by CT scans, spiral CT scans, or MRI testing, sure, but these tests buy you no additional life even if the disease is detected. These sad cases usually arise because some well-intentioned family who lost a loved one donated a good deal of money to a cause without really understanding the science behind it.

Moreover, most treatments can produce debilitating or fatal side effects in a fraction of the people taking them. Therefore, when we examine the effectiveness of a treatment at extending human life expectancy, we have to consider that the treatment can prolong life in one way but reduce life expectancy in another way. Thus, the real-world effects may be smaller than the efficacy of the treatment would suggest.

Side effects from an otherwise very good drug can also reduce the chances that a person will take the drug in the real world. In the published experiment (where people in white coats were watching participants take their medications) the efficacy of such a drug will appear to be quite good in print. But in the real world it may produce little benefit because so few people want to take it. **Effectiveness** indicates how well such tests, treatments, or programs perform in the real world.

By providing data on effectiveness, cost-effectiveness analysis provides information on how interventions are likely to work in everyday use. While supplementing cereal grains with the vitamin folate may greatly reduce neural tube defects in newborns, it may also lead to the underdiagnosis of vitamin B<sub>12</sub> deficiency among poor or elderly populations (Haddix, Teutsch, Shaffer, & Dunet, 1996). When vitamin B<sub>12</sub> deficiency is not diagnosed and treated early, it too can lead to severe complications. Thus, the efficacy of a given treatment in preventing a disease may not be representative of its overall effectiveness at preventing death due to that disease.

## The Reference Case Analysis

Cost-effectiveness analysis can take many subtly different forms. Consider the case of a local health department that wishes to know the cost of screening people for tuberculosis in its clinics. It may examine the cost per case of active tuberculosis prevented when patients are screened in its clinics (relative to not providing these screening exams). This type of analysis would furnish the health department with information useful for making specific internal decisions, such as whether it is worthwhile to spend money on such programs. However, it would not provide a good deal of information on the overall benefits of screening to the population it serves. This is because it does not provide any information whether it is more valuable to treat a case of tuberculosis or better to invest in some other disease.

Or the health department may wish to expand the analysis in order to obtain information on both the cost-effectiveness of its operations and its broader mission of improving the longevity of the population it serves. For instance, it may wish to determine the cost of the program per year of life saved as well as the cost per case prevented. This would also provide information for internal decision making and on how the programs are benefiting the populations that they serve.

Finally, tuberculosis is a severe disease that can require burdensome treatments and long stints in hospitals (sometimes in an isolated room), and it can have an impact on people's quality of life. The health department may therefore also wish to examine the cost of tuberculosis screening relative to improvements in the quality and quantity of life of the population it serves. This type of information would allow them to assess the impact of tuberculosis on mortality. It would also allow them to compare the cost of tuberculosis screening programs to programs that predominantly affect the quality of life, such as mental health programs.

While some health events, such as high-rise construction accidents, predominantly affect the quantity of life, others, such as repetitive stress injuries at work, predominantly affect the quality of life. When a measure of quality of life is added to a cost-effectiveness analysis, it becomes possible to compare health interventions across the spectrum of disease. (Recall that one QALY is a year of life lived in perfect health.)

The ability to make comparisons across different diseases opens up the possibility of standardizing cost-effectiveness analysis, so that the incremental gains associated with virtually any intervention can be compared with those of another. If the health department conducted its analysis based on the cost per active case of tuberculosis prevented, it would provide some

information on how the new intervention compares with what it is doing now. But it wouldn't be able to compare its new intervention with other programs in the health department because the denominator is different. If it used life expectancy, the denominator would be the same. Therefore, it could compare the cost per life saved of the tuberculosis program with a program that aimed to prevent window falls.

But you would still miss the boat. A program designed to reduce repetitive stress injuries at work wouldn't save many lives. Therefore, no matter how good the program is, it will always seem less cost-effective than a program designed to prevent window falls. Here again, the QALY saves the day. By comparing interventions across a term that captures both quantity and quality of life, it becomes possible to measure the relative cost-effectiveness of each program in the health department—provided that costs, quality measures, and life-years gained are all calculated in a similar way in each of the analysis. Under these conditions, it is possible to compare the incremental cost per QALY gained for health interventions as different as vaccination and migraine prevention. Of course, you need a standard set of methods to refer to if you are going to do this. This more or less standardized set of methods is called the **reference case analysis** (Gold et al., 1996; Neumann et al., 2016).

The use of disparate approaches to cost-effectiveness analysis sometimes leads to widely different study results. For example, in the introduction to their book, the first Panel on Cost-Effectiveness in Health and Medicine notes that the published cost-effectiveness of screening mammography for the detection of breast cancer varies from cost saving to \$150,000 per life-year saved (Gold et al., 1996; Neumann et al., 2016). (In that example, we adjusted the cost to 2017 US dollars so that you can get a better idea of what the range would look like today.) This huge variation was due to differences in what was and what was not included in the analysis. The panel set methodological standards for conducting cost-effectiveness analysis in hopes of preventing this kind of variation in cost-effectiveness ratios. Thus, the **reference case** was born.

The reference case standardizes the types of costs that should be included and requires the use of the QALY as the unit of effectiveness to ensure that all studies have comparable outcomes. The reference case also requires that two analysis be performed. In one analysis, the study must include all costs (regardless of who pays). In the second analysis, it requires the use of costs specific to the health sector. In this book we focus on reference case analysis.



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**FOR EXAMPLE: WHAT'S IN A NAME?**

A lot of fuss is made over the distinction between *health* interventions and *medical* interventions (Gold et al., 1996; Neumann et al., 2016). *Health* generally refers to public health programs, such as the provision of clean water or laws requiring grains to be fortified with vitamins. *Medical interventions* specifically refer to things that medical providers do, such as selecting the most appropriate antibiotic. In practice, the distinction is blurry. For instance, checking blood pressure might be considered a health intervention if it is done as part of a screening program, but a medical intervention if it is done to ensure that a patient is receiving the proper dosage of medication. In this book, we usually refer to both types of interventions under the general heading of “health.”

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Why would you want to conduct any type of cost-effectiveness analysis besides the reference case analysis? Consider the health department used as an example at the beginning of this section. If the department is interested only in internal decision making, a reference case analysis would provide superfluous information, such as private sector costs and patient costs. Therefore, a reference case analysis is not necessarily the best approach in all situations. (For more information, see “A Note on Methods” in the Preface to this book.)

You now should have a sense of what cost-effectiveness is, why it is important, and for whom it is important. In the next section, we move on to how cost-effectiveness analysis is used to make policy decisions in health.

## **Cost-Effectiveness Analysis and Policy**

We have noted that cost-effectiveness analysis are used primarily to compare different strategies for preventing or treating a single disease (such as tuberculosis). In addition, they can be used to maximize the quantity and quality of life within a given budget. In this section, we briefly explore how policy decisions are sometimes made using cost-effectiveness analysis, as well as some of the controversies that have arisen as a result of such policy decisions.

### **Prioritizing Health Interventions**

It is possible to use cost-effectiveness analysis to purchase the most health under a fixed budget. If the incremental cost-effectiveness of everything that

is done in medicine were known, we would have a sense of the opportunity cost of any health investment we might make (Jamison, Mosley, Measham, & Bobadilla, 1993). It would therefore be possible to list all interventions in a table and then draw a line between what is and is not affordable. When incremental cost-effectiveness ratios for different interventions are listed in a table, it is sometimes called a **league table** (Mauskopf, Rutten, & Schonfeld, 2003).

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### FOR EXAMPLE: COST-EFFECTIVENESS IN DEVELOPING COUNTRIES

Nowhere else is cost-effectiveness analysis more important than in developing countries. With annual health budgets as low as \$5 per person, efficiency is critical. Recognizing the need for better health purchases, the World Health Organization developed CHOosing Interventions that are Cost-Effective (CHOICE). CHOICE is a program that contains information on costs, mortality, quality-of-life measures, and completed cost-effectiveness analysis for each region of the world (<http://www.who.int/choice/en/>).

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League tables can also be used to place a given intervention in context. For instance, suppose we know that mammography costs \$30,000 per QALY gained relative to no mammography. We can't be sure whether this is expensive or cheap relative to other things done in medicine. However, suppose we know that treating an otherwise fatal bacterial pneumonia with a commonly used antibiotic costs \$25,000 per QALY gained relative to no treatment. Then we know that \$30,000 per QALY gained for mammography is in the ballpark of a treatment that most would agree should not be denied. But if treating bacterial pneumonia were found to cost \$300 per QALY gained and heart-lung transplants in active chain smokers were found to cost \$15,000 per QALY, then perhaps mammography wouldn't be such a reasonable thing to do. We should, instead, invest in treating pneumonia and heart-lung transplants.

Let's take a look at how else a league table might be used. Table 1.1 represents a hypothetical league table for a village in Malawi with a total health budget of \$58,000. In this table, we rank a number of interventions by their incremental cost-effectiveness ratio relative to not providing the treatment at all. This ratio tells us how much it costs to buy one year of perfect health.

If we know the size of the affected population and the total cost of the intervention, we know how much we will spend per year on any given strategy and the total number of QALYs we'll save. In this case, we only have \$58,000, so we can't even provide the first four treatments, which

**Table 1.1** Hypothetical League Table for a Village in Malawi with a \$58,000 Health Budget

<b>Intervention</b>	<b>Incremental Cost-Effectiveness Ratio<sup>a</sup></b>	<b>Size of Affected Population</b>	<b>Total Cost per Year</b>
Measles vaccine	\$375	5,000	\$15,000
Sexually transmitted disease treatment	\$420	300	\$2,100
Pneumonia treatment	\$428	150	\$1,800
Mosquito nets	\$846	22,000	\$44,000
HIV treatment	\$3,000	100	\$30,000
Total			\$92,900

<sup>a</sup>The reference intervention is to do nothing.

collectively cost nearly \$63,000. We might use this table to advocate for more funding or to figure out how we might reassess our interventions. For instance, prioritizing mosquito bed nets for children, who have not yet developed immunity to malaria, may be more cost-effective than providing them to family members who are older and less likely to succumb to the disease.

### *Exercises 3 and 4*

3. How many QALYs will \$1,000 worth of measles vaccine purchase in this village (the ICER for measles vaccine is \$375 per QALY gained)?
4. A nongovernmental organization geared toward providing mosquito nets comes to a similar village in Malawi to the one represented in Table 1.1. This village has no health budget but wishes to provide \$1,000 worth of mosquito nets (the ICER for mosquito nets is \$846 per QALY gained). How many QALYs will be forgone as a result of spending the money on nets rather than on the measles vaccine?

However tempting it might be to create a list of interventions based on their cost-effectiveness, decisions surrounding the allocation of social resources cannot be made based on numbers alone. For example, HIV medications in Table 1.1 purchase a large amount of health for a small group of people, which might not be seen as fair for the village as a whole. Cost-effectiveness analysis does not provide ethical information; it is just one handy tool policymakers might use when deciding on which interventions they will fund (Gold et al., 1996; Neumann et al., 2016). (Other examples of league tables can be found at: <https://research.tufts-nemc.org/cear4/>. From there, navigate to League Tables. (For further discussion, including the limitations of league tables, please see Mauskopf et al., 2003.)

### **FOR EXAMPLE: CHILE'S STORY: HOW TO SUCCEED BY NOT BEING COST-EFFECTIVE**

Chile created a national health plan, called the Universal Access with Explicit Guarantees (AUGE) program, that in part used a league table to achieve its policy objectives. The idea was to start covering a small number of conditions and then scale up the program as time went on. Rather than choose the most cost-effective interventions to start with, however, those who designed the plan deliberately chose inefficient but heartwarming treatments, such as chemotherapy for children. The result? An astounding success: The president invited the cured children and other patients for a press conference to tout the success of the program. This single media event defeated the resistance of insurance companies and the national medical association. In 2013, the Ministry of Health increased the number of priority health conditions from 66 (in 2010) to 80. The AUGE program demonstrated that prioritization of treatment is multidimensional and does not rely on a single factor (e.g., cost-effectiveness). Instead, other criteria are used for coverage decisions such as high costs, social consensus, rule of rescue, inequality, effectiveness, capacity of the healthcare system, and burden of disease (Bitrán, Escobar, & Gassibe, 2010; Frenz, Delgado, Kaufman, & Harper, 2013; Vargas & Poblete, 2008). This is how cost-effectiveness analysis are meant to be used—as important pieces of a complex policy decision.

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### **Do Cost-Effectiveness Analysis Actually Change the Way Things Are Done?**

Examples of policy decisions that have been influenced by cost-effectiveness analysis include strategies for reducing parasitic infections in immigrant populations (Muennig, Pallin, Sell, & Chan, 1999), conducting cervical cancer screening among low-income elderly women (Fahs, Mandelblatt, Schechter, & Muller, 1992), and adding folate to cereal grains in the United States (Haddix et al., 1996). These studies appear to have sparked changes in the way that patients received medical care in local health departments, changes in Medicare reimbursement policies, and changes in the rules set by the U.S. Department of Agriculture. Still, although Canada, Australia, and a number of European countries use cost-effectiveness to help decide what should be paid for and what should not, Medicare has not yet officially incorporated cost-effectiveness analysis into its payment policies (Neumann, Rosen, & Weinstein, 2005).

Cost-effectiveness analysis can also lead to policy changes with broader implications than the authors intended. For instance, when supplementing

cereal grains was found to be a cost-effective strategy for preventing neural tube defects in the United States, not only did cost-effectiveness analysis help convince the food industry that it was worth the cost, but other countries also considered similar interventions (Schaller & Olson, 1996; Wynn & Wynn, 1998).

Cost-effectiveness analysis has also proven to be a controversial tool when used without taking the broader social implications of health interventions into account. For example, in the state of Oregon in the United States, cost-effectiveness analysis was used to prioritize health interventions paid for by the state government using a league table. Those interventions deemed unaffordable were not paid, creating a large statewide and national outcry from groups denied treatment on these grounds. Some of the cost-effectiveness rankings seemed unintuitive when taken on face value. For example, braces for crooked teeth were ranked higher than treatments for Hodgkin's disease. (Hodgkin's disease is one of the few curable cancers.) In addition, the cost-effectiveness computations used to determine the priority list resulted in unintuitive ranks where having crooked teeth was ranked higher than Hodgkin's disease (Oregon Health Services Commission, 1991; Oregon Office for Health Policy and Research, 2001; Penner & McFarland, 2000).

These real-world examples highlight some of the promises and pitfalls of cost-effectiveness analysis for policy. Students embarking on this endeavor may one day find themselves facing tough ethical decisions for which there is no right answer. For instance, you may be working for a government that wishes to base immigration policies on preexisting conditions for applicants. Or you might be working for an insurance company that wishes to deny an effective treatment based on its cost-effectiveness. In such instances, consultation with all stakeholders (physicians, policymakers, payers, and patients) can help you come up with a strategy that better balances everyone's needs. In practice, this is not always easy to do, and oftentimes you are required to make decisions with only the best available evidence on hand.

To end this section on a positive note, though, let's return to Oregon for a moment. Recently, researchers and policymakers collaborated to put Medicaid to the test. Excess funds were used to randomly assign thousands of participants to either receive the opportunity to sign up for Medicaid or to receive whatever medical care they were already managing to scrounge up. The study started a political firestorm because it found that, while Medicaid increased preventive screening, produced financial protections, and reduced depression, it did nothing to actually improve physical health (Baicker et al., 2013). Medicaid opponents therefore argued that Medicaid

should be cut. Why is this a happy note? Cost-effectiveness analysis showed that these other benefits actually make Medicaid more than worth the initial investment (Muennig, Quan, Chiuзан, & Glied, 2015).

## What Does the Future Hold?

Cost-effectiveness is all fine and well, but most patients in the United States don't want to be told that they can't get an annual physical with their doctor because it isn't "cost-effective." (In fact, not only is it expensive and not helpful, annual physicals may actually be harmful because the doctor can find things that are not a problem and might even eventually require invasive procedures to detect these phantom ailments.) Since insurers already charge patients part of the medical bill to reduce the cost of care (a fee called a "copayment"), one fix to this problem is to just charge less for cost-effective care and more for cost-ineffective care. Of course, we need a good jargon-y name for any such thing, and this idea has a good one: "value-based insurance design" (Fendrick, Smith, Chernew, & Shah, 2001). Several providers have implemented this approach, and preliminary data show that it saves money (Farley, Wansink, Lindquist, Parker, & Maciejewski, 2012; Frank, Fendrick, He, Zbrozek, Holtz, Leung, & Chernew, 2012; Maciejewski, Wansink, Lindquist, Parker, & Farley, 2014).

The Patient Protection and Affordable Care Act (PPACA), more commonly known as "Obamacare," was written into law in 2010. Obamacare is actually a long list of incremental changes to the U.S. healthcare system that are supposed to add up to something big. One such change is to set up a Patient Centered Outcomes Research Institute (PCORI). This institute funds research that will guide patients and providers toward making more informed decisions. PCORI is tasked with performing *comparative*-effectiveness research; that is, it is prohibited from using the dollars per quality-adjusted life-year metric in determining thresholds for selecting the most cost-effective strategy (Neumann & Weinstein, 2010). In other words, the U.S. approach suggests that one should always select the most effective treatment no matter what the cost. Of course, there is no such thing as a bottomless budget. So this approach ends up costing lives by paying for things that we can't afford at the expense of those things that we can.

This is in contrast to other countries, such as the U.K.'s National Institute for Health and Care Excellence (NICE), which use cost-effectiveness analysis to determine coverage decisions for pharmaceutical agents and new technologies. Similarly, Canada and Australia have established agencies that evaluate the submission of pharmaceutical agents for inclusion

into the public formularies. In Canada it is the Common Drug Review, and in Australia it is the Pharmaceutical Benefits Advisory Committee. These agencies play critical roles in controlling expenditures, while maintaining or increasing the overall societal values of new pharmaceutical agents. The advantage to these approaches versus the one adopted by the United States is that they can save more lives within a fixed budget. Nice!

Still, public debates over cost-effectiveness have given the field a bit of a black eye. This is unfair in part because those making the argument are ill informed and in part because it is difficult to defend something so complex. After all, you can't win a rhetorical war when you first have to explain the incremental cost-effectiveness ratio. Unlike cost-effectiveness analysis, however, comparative-effectiveness analysis is in theory more individualized. While cost-effectiveness analysis just provides information on what is best for the average person out there, comparative-effectiveness considers "effectiveness, benefits, and harms of treatment options" for the *individual*, not just the average person (Agency for Healthcare Research and Quality, 2015). This does not eliminate the need to evaluate cost; however, it does limit how we use the results from comparative-effectiveness research when making decisions about which treatment options provide the overall greatest benefit to patients, providers, and society.

As future studies on comparative-effectiveness research incorporate cost, the debate will once again return to the question of rationalizing health care and its inherent moral and ethical (and political) problems. Currently, there is great interest in identifying the strategy with the highest value but at the lowest cost. Cost-effectiveness analysis is an important tool for carrying out this task.

Another thing that the future might hold is that cost-effectiveness analysis could increasingly be applied to social policies rather than just comparing medical treatments. This is exciting, because many nonmedical investments that the government makes actually produce health and might do so with more value than investments in the medical system itself (Muennig & Woolf, 2007; Woolf & Aron, 2013). The great upside of this is that governments could make the best use of all of the taxpayer money that is spent. The downside is that modern cost-effectiveness research protocols don't teach students how to actually do these types of studies.

One important difference is that, like new drugs, social policies can produce unintended "side effects." For instance, many policymakers respond to road congestion by building more roads (Sterman, 2006). Road congestion is a terrible problem because people waste a lot of their precious time sitting in their cars while polluting the air and warming the planet. The problem with building more roads is that it increases the demand for cars.

Not only do more people drive, but cities tend to sprawl outward as people have access to cheaper property in the suburbs and exurbs. So people spend more, not less, time in their cars as more roads are built. In addition, accidents, obesity, and pollution tend to get worse than they would have had the money been spent on public transit instead. Unlike a cost-effectiveness analysis of a drug that has been tested using randomized controlled trials, these unintended consequences are not known and must be thought out. However, they can also be modeled using specialized software.

The “science” of thinking these problems out is known as *complex systems dynamics*, among other titles. Throughout this book we will slowly introduce this very cool science to you.

## Summary

Due to the increasing costs and limited resources of health care, there had to be some way to objectively determine how much health care we can afford to provide while maintaining (or enhancing) its quality. Cost-effectiveness analysis combines health interventions, competing alternatives, health states, health status, costs, and benefits (e.g., QALYs) in order to calculate the incremental cost-effectiveness ratio, the difference in cost needed to realize an incremental gain in benefit between two strategies. This provides us with a guide to help make coverage decisions for pharmaceutical drugs and costly interventions. However, making these decisions is a multidimensional task and requires us also to consider social preferences, burden of disease, and the capacity of the healthcare system.

## Further Readings

Those who are interesting in reading more about Value-Based Insurance Design are encouraged to visit the Center for Value-Based Insurance Design hosted by the University of Michigan (<http://www.sph.umich.edu/vbidcenter>).

David M. Eddy (Eddy, 1991a, 1991b, 1991c) and Thomas Bodenheimer (Bodenheimer, 1997a, 1997b) wrote several papers about the early phases of the Oregon State Health Plan.

For more information regarding Chile’s Health Plan Reform and AUGE, please refer to Vargas and Poblete’s review. It provides an excellent explanation of prioritization by Chile’s Ministry of Health (Vargas & Poblete, 2008).



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