

Chapter 2

Bioengineering and Technology Assessment



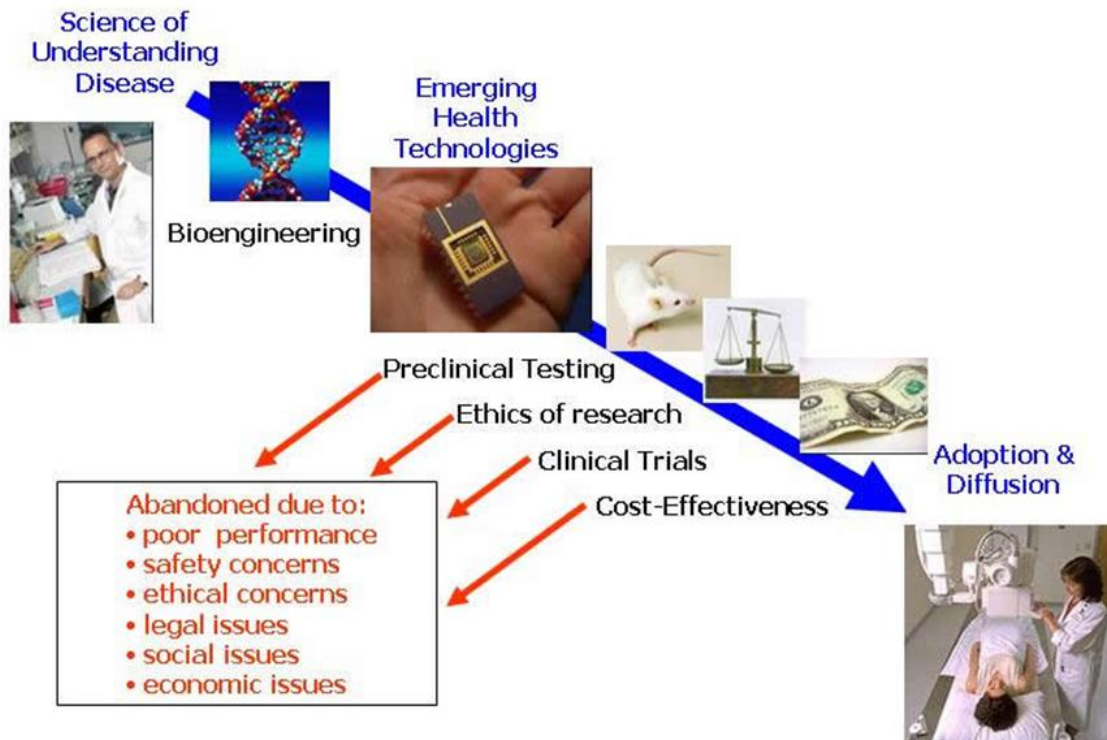
In Chapter 1, we examined the development and introduction of a new technology that initially appeared as if it could provide new hope to women with advanced breast cancer. Small clinical trials showed that women with high risk or metastatic breast cancer treated with high dose chemotherapy and bone marrow transplant (HDCT+BMT) had substantially better response rates and survival compared to historical experience with standard chemotherapy. These early promising results were widely publicized, and even though the therapy had serious side effects, it was used to treat thousands of women. Usually, before a new technology is adopted, randomized clinical trials are conducted to compare the performance of the new technology to that of existing technologies. In such randomized clinical trials, patients are randomly selected to receive either the current standard therapy or the new therapy; outcomes such as response rate, survival and side effects are then compared for the two groups of patients. However, because patient demand was so high for HDCT+BMT, randomized clinical trials took much longer to complete than planned. Ultimately, randomized clinical trials showed that HDCT+BMT did not improve survival for most patients. The promising results of early trials were misleading due to a combination of factors, including their small size, selection bias and scientific misconduct.

The case study of HDCT+BMT for advanced breast cancer underscores the need for a systematic method to guide the development and introduction of new technologies. In Chapter 1, we saw how the interplay of desperate patients seeking the best treatment, early media publicity and a scientist who falsified data all combined to slow the progress of medical science. In the end, many patients unnecessarily underwent an expensive and highly toxic therapy. How can we prevent this from happening with future technologies? In this chapter, we will consider the methodology of technology

assessment, which provides a systematic set of tools to determine the performance of a new technology and to assess the impact of using the technology both for individual patients and for society as a whole. When used properly, technology assessment can help ensure that new medical technologies are introduced on the basis of sound scientific evidence and not simply on the opinions of physicians and scientists or the hopes of patients.

As a prelude to technology assessment, we consider the steps involved in bringing a new technology from the laboratory bench to the patient's bedside. **Figure 2.1** shows a roadmap of this process. Bioengineers build on the scientific understanding of a disease to design new healthcare technologies. New technologies must be rigorously tested to determine whether they are safe and effective. This testing process can include preclinical testing in cell or animal models, as well as testing in human subjects. These tests must be carried out in an ethical manner. In addition, an important consideration in the adoption of new technologies is whether they are cost-effective. The process of health technology

Figure 2.1: A roadmap of the health-care technology development process. Technology assessment spans the entire range of development activities.



assessment spans all the steps in the healthcare technology development process, from lab to patient.

The Littenberg Method of Technology Assessment

Benjamin Littenberg proposed a model of technology assessment that is particularly useful for new technologies.[1] The Littenberg method asks five questions regarding a new medical technology:

- *Biologic plausibility*: Does our current understanding of the biology of the disease in question support the use of the technology?
- *Technical feasibility*: Can we safely and reliably deliver the new technology to the target patients?
- *Clinical Trials*: Do the results of randomized clinical trials comparing the new technology to current standards of care show a benefit?
- *Patient outcomes*: Are patients better off for having used the new technology?
- *Societal outcomes*: What are the costs and ethical implications of the technology?

It is useful to consider our case study of HDCT+BMT in the context of the Littenberg model to see whether the technology was assessed appropriately at each level and whether that assessment supports the use of the technology.

Biologic Plausibility: Many scientific studies supported the promise of HDCT+BMT. In particular, as the dose of chemotherapeutic agent was increased to treat women with breast cancer, response rates increased. Based on these data, physicians believed patients with advanced breast cancer would benefit from doses of chemotherapy so high that it would destroy bone marrow.

Technical Feasibility: Mortality rates were initially quite high for breast cancer patients treated with HDCT+BMT, despite the advances in leukemia treatments showing that bone marrow transplantation could be safely performed. However, as more women were treated and regimens were refined, mortality rates dropped substantially, improving technical feasibility. Thus initially HDCT+BMT was supported by both biologic plausibility and technological feasibility, the first two criteria of Littenberg's method.

Clinical Trials: There were many small, clinical trials carried out to assess the effectiveness of HDCT+BMT; however,

Read more about the Littenberg Method:

The Littenberg method of technology assessment is defined in this article and used to analyze screening tests for hypercholesterolemia. [1]

Littenberg, B. Technology assessment in medicine. *Academic Medicine*, 67(7), pp. 424-428



CDC

Figure 2.2: Multiple clinical trials have proven mammography to be effective for screening for breast cancer in women.

these trials were not randomized clinical trials. As we will see later, a randomized clinical trial is the strongest source of scientific evidence to assess whether a new technology is effective compared to current standards of care (**Figure 2.2**). The tragedy of HDCT+BMT was the delay of completing randomized clinical trials, due to political and media pressures and scientific misconduct. By the time clinical trial results seriously questioning the benefit of HDCT+BMT compared to standard chemotherapy were available, many women had already undergone the treatment.

Patient outcomes: Were women better off in the long term for having been treated with HDCT+BMT? The early clinical trials assessed only response rates to therapy; later trials examined survival. In assessing patient outcomes it is important to consider both short term outcomes (e.g. response rates) and long term outcomes (e.g. survival) as well as quality of life issues. Clearly, patients treated with HDCT+BMT experienced a quality of life that was initially lower because of the side effects of the treatment. In the end, randomized trials showed that survival rates were not substantially higher than those for standard treatment.

Societal Outcomes: Was society better off for having used HDCT+BMT? The new technology was substantially more expensive than standard chemotherapy while adding no additional survival benefit. If HDCT+BMT had showed clinical benefit compared to standard therapy, then society would have to consider the difficult question of whether the increased benefit is worth the additional cost.

Thus, HDCT+BMT was not supported by the final three criteria of the Littenberg method, a conclusion that puts the effectiveness of the technology in serious doubt. Clearly, HDCT+BMT technology was not adequately assessed before entering widespread use, a failure that led to many women receiving a painful treatment that offered fewer benefits than initially believed.

Important Vocabulary of Technology Assessment:

In the rest of this chapter, we will outline in more detail the methods of technology assessment. They will guide our thinking as we examine new technologies throughout the rest of the text. We begin with definitions of some important terms. Technology does not necessarily involve sophisticated or expensive James-Bond-like gadgetry or devices. Health care technology can be any intervention to promote health, including specific tests or treatments as well as systems that aid in the delivery of health care. The technology

Challenges of Anti-Retroviral Drugs: June 13, 2007**Rachel****Botswana**

As we will see in Chapter 4, Patients who are HIV positive are treated with drugs called anti-retrovirals or ARVs. Often, patients must follow complex regimens of drugs. The situation is further complicated for HIV positive children, because drug companies currently do not make ARVs in pediatric doses. So often parents must split pills in half to ensure their children receive the correct dosage. Patients must adhere closely to the schedule of taking their ARVs or HIV can develop resistance to the drugs. This is a major challenge in treating HIV/AIDS today.

I was thinking of different ways to help AIDS patients and I thought that a seven-day AM/PM pillbox would be useful. (I have used them, and I remember my grandmother used them for her multitude of pills) Then at the beginning or end of every week, the patient or the caretaker can put all the pills (and half pills) in the proper compartments. Although this unfortunately excludes all the people who need to take syrups, I was talking with one of the patients who came in for a guide yesterday about adherence and she said it would help. She has a son in his teenage years and, while she gives him the pills most of the days, sometimes he goes out to play football (soccer) with his friends and forgets to take the pills with him. When I asked about how he would feel carrying around a pill box, and if he was comfortable taking it around his friends, she said that he didn't mind and that some of his friends were on ARVs as well. I am getting a mixed view on exactly how prevalent or entrenched the stigma for AIDS really is. Driving down from Choebe this weekend, even in the smaller towns there were billboards about AIDS encouraging testing, a large ad for condoms, and a free condom box at the passport immigration. I also saw the first abstinence billboard, which seemed almost to contradict the "get tested" billboard on the opposite side of it.



can address any component along the health care continuum: **prevention, screening, diagnosis, treatment, or rehabilitation**. In this text you will see examples of technologies ranging from simple childhood vaccinations to prevent disease to complex total artificial hearts to treat end stage heart disease. While the complexity of the technology can differ dramatically, the process of health care technology assessment is the same.

The ultimate goal of health technology assessment is to inform decision making, whether it is done from the perspective of an individual patient or from the larger perspective of society. The underlying questions which health technology assessment needs to address include the following[2]:

- What is the clinical impact of the intervention?
- What is the cost of the intervention?
- What is the clinical impact of the intervention weighed against its cost?

In order to answer these questions, it is necessary to evaluate the safety, effectiveness, cost-effectiveness, and the social, ethical, and legal impacts of a technology.[3] In this evaluation, we must consider both the direct and indirect consequences of using a health technology.

Direct consequences of a health technology are the **intended benefits and costs**.[3] For example, if we develop a new, more accurate cancer screening test, the intended benefits include factors such as the accuracy of the test and the number of late stage cancers that could be prevented through early detection if the new test is widely adopted. The intended costs include the cost of the test, as well as the savings that would result from being able to treat patients for early stage cancer, which is less expensive than treatment for late stage cancer. In rare cases, the savings associated with a technology can actually be greater than the costs of using the technology. We will later see that this is the case with some childhood immunizations.

The indirect consequences of a technology are the unintended economic, social, or other technology effects.[3] Let's imagine that our screening test is somewhat invasive and patients perceive it to be much more uncomfortable than the previous screening test. As a result, some patients who would have been screened with the old test now avoid cancer screening altogether, because of fear or embarrassment. In this case, the introduction of a new and more accurate test can actually decrease screening effectiveness be-

Prevention: Health interventions designed to prevent a patient from developing disease.

Screening: A test given to members of a defined population, not necessarily at risk for a disease, to identify those individuals who are most likely to be helped by further tests to diagnose the disease.

Diagnosis: The identification of disease through signs, symptoms, imaging, bloodwork, cultures, cytologic sampling, or biopsy.

Treatment: A health intervention to cure disease or to reduce symptoms of disease.

Rehabilitation: The process of restoring skills lost to illness or injury.

Examples of Benefits and Costs of Prostate Cancer Screening:

Monitoring the level of prostate specific antigen (PSA) is frequently used to screen older men to determine if they are likely to have prostate cancer. Invasive diagnostic testing is performed to determine whether men with elevated PSA levels have prostate cancer requiring therapy.

Intended Benefits: Screening can identify men with prostate cancer at an early stage, when it is still curable.

Intended Costs: The cost of a PSA exam is less than \$100.

Unintended Costs: Because prostate cancer grows slowly, the new test can identify men with prostate cancer that will never cause any symptoms. These men undergo further invasive, painful testing and treatment which may be unnecessary.[4]

cause patient adherence to physician recommendations decreases. Health technology assessment must account for such unintended consequences.

As such, health technology assessment is a bridge between the basic research and development of a technology and its real-life application. In the ideal world, technology assessment provides an opportunity to assess the technology's effects *before* its widespread introduction, but in many cases it is used to analyze mature technologies already in routine clinical use to suggest strategies to use limited healthcare resources more effectively.

When Do We Assess Technology?

A key question in health technology assessment regards the timing of when to perform a technology assessment. When health technology is assessed early, there are increased benefits, including potentially protecting public safety and identifying which populations should use the technology. However, assessment in the earlier stages also has risks. A health technology may not yet be perfected, and the populations for whom the technology should be used might not be appropriately identified. In addition, in an early assessment the data available about the performance of the technology are more likely to come from clinical trials rather than the settings where it will be routinely used. This can be a problem because clinical trials are often carried out by experts under well-controlled conditions and may overestimate the performance of a technology in the community setting.

We have a special vocabulary to describe this change in performance. Efficacy refers to the performance of a technology under ideal, controlled conditions. Efficacy is studied in homogeneous populations by using standardized procedures under ideal testing conditions by expert practitioners. Effectiveness is the measure of performance in a normal clinical setting. Effectiveness is studied in heterogeneous populations, and the technology is implemented by ordinary practitioners under conditions of routine clinical care.[5] Often the efficacy of a technology is much higher than its effectiveness, because the same experts that developed a test are using it under the best circumstances. If a health technology assessment is carried out using efficacy data, then the assessment lacks critical information about how the technology will truly perform in the real world. The true effectiveness, or impact, of the technology cannot be known until the technology has widespread use.

The argument for later evaluation also has advantages and

disadvantages. A later evaluation of technology will have more data, particularly regarding effectiveness, but the data may be biased. For example, if the technology has already been dispersed widely, then a randomized clinical trial may not be ethically feasible. If the initial effectiveness of the technology is favorable, researchers face an ethical dilemma by intentionally withholding the treatment to trial participants in the control group. Potential participants are also less likely to accept randomization in such a trial if significant benefits have already been demonstrated. Additionally, by the time a health technology assessment is completed the technology may already be outdated, either in how it is specifically used, or because superior alternatives for the given clinical problem have been identified.

Thus, the timing of health care technology assessment is a “moving target” problem with no obvious answer. It is for this reason that health technology assessment should be an iterative process, done on an ongoing basis to achieve evaluations throughout the life cycle of the technology development process.

Metrics of Health Technology Assessment

Many times, a ratio of benefit to cost will be calculated as a quantitative metric of technology assessment. It is important to point out that the decision regarding the usefulness of a technology cannot be made in a vacuum. In other words, it must be recognized that when health technology is assessed, one must think about the relative benefits and costs involved in the clinical situation. There is always an alternative to a new health technology being assessed. Alternatives include currently used treatments or technologies, termed the standard of care. Both the standard of care and the new technology have economic costs and clinical benefits that must be taken into account. Ranking strategies according to their benefit to cost ratio can often be a helpful way to compare the effectiveness of different approaches, including new technologies, the standard of care and “do nothing” strategies.[7]

Collecting Data for Health Technology Assessment:

Where do we obtain data about the costs and benefits of health care technologies? Generally data come from clinical trials – well controlled experiments designed to compare the performance of two technologies. In carrying out health technology assessment, we can obtain secondary data about a technology from published literature describing clinical trials, or we can collect primary data by carrying out our

Technology Assessment in Developing Countries:

Technology assessment is particularly important in settings where health care resources are extremely limited, such as developing countries. Unfortunately, few developing countries have health technology assessment programs.

The results of technology assessment applied in different settings cannot simply be used in developing countries—many factors, such as whether a disease is common or rare, the social acceptability of a technology, the efficacy of a technology and the cost—vary dramatically throughout the world. [6]

own clinical trial. Primary data can be analyzed for efficacy, effectiveness, safety, reproducibility, patient satisfaction, and cost-effectiveness. Secondary data can be also be used to assess the same outcomes – either by using data from one published study or by using meta-analysis, a statistical method that combines data from different studies to estimate the overall effect of an intervention on a specific outcome.[5] As we will see throughout this text, carrying out a clinical trial can be an expensive task; if we want to examine long term outcomes, we may have to wait decades for results. Many times we want to carry out a health technology assessment without waiting this long. As an alternative, we can write a computer program to simulate the clinical trial. This process is called decision analysis. In decision analysis, we simulate the likely outcomes from a group of hypothetical patients, using probabilistic methods.[5] Data from primary and secondary sources are used to estimate the efficiency of a technology as well as likely patient outcomes. The computer program follows each group of patients over time, using these data to “roll the dice” for each patient at important time points. Decision analysis can provide a very quick and inexpensive way to estimate what might happen in a clinical trial without having to spend millions of dollars and wait decades. However, it is not a substitute for actually carrying out a clinical trial.

There are many types of clinical trials that can provide useful data for health technology assessment. Nonrandomized clinical series often provide data on the efficacy of a technology. Randomized clinical trials, where participants are randomly divided into an experimental group receiving the new technology and a control group receiving existing technology, should be used to compare the performance of the new technology to the existing technology. In the hierarchy of information, randomized clinical trials are considered the strongest study design.[8] Randomized clinical trials may not be necessary if the patient benefit from the test is so dramatic as to leave little room for doubt that the new technology is as good or better and less expensive than existing options. However, few technologies meet those criteria.

Policy decisions and HTA

How is a health technology identified as a candidate for assessment? How do the results of health technology assessment affect the use of a technology? Who monitors health technology assessments? These are all crucial policy questions that are just as important as the scientific methodology of health technology assessment. As mentioned earlier, the

purpose of health technology assessment is to aid and inform decision making regarding the use of a technology. It is important then to understand not only how a technology is assessed, but also what is then done with that assessment.

Often emerging technologies surface through reports in the literature of a series of cases. Once an existing technology has been accepted as standard clinical practice, its use can be tracked with data obtained from health registers and institutional and organizational databases, and by use of national administrative and financial data and post-marketing surveillance data. Often policy decisions about the use of existing technologies are then made by group judgment methods (e.g. **consensus conference**).[9] Social and ethical issues should be considered throughout the development of a technology.

The U.S. and Canadian Preventive Services Task Forces, which make recommendations about clinical preventive services, have devised a hierarchy of evidence upon which to base recommendations. The hierarchy has two determinations: quality of evidence and strength of recommendation. [4] The Task Forces categorize the overall *quality* on a three point scale divided into good, fair and poor. Good evidence is derived from well designed, well conducted studies in representative populations that directly assess effects on health outcomes. While fair evidence is sufficient to determine effects on health outcomes, the strength of the evidence may be limited by number, quality, or consistency of the studies, Poor evidence is considered insufficient to assess the effects on health outcomes due to a limited number of studies or flaws in the study design. The strength of recommendation is divided into five categories: there is good, fair, or insufficient evidence to support the recommendation that the test *not* be used in periodic health examinations, and there is fair or good evidence to support the recommendation that the test be used in periodic health examinations. This hierarchy has been applied by many technology assessors. Not all procedures apply to the periodic health examination, but the concept of using evidence to justify the strength of a recommendation is logical.

The most recent **Clinical Preventive Services Guidelines** include recommendations for several tests we will examine later in this course.[4] For example, the current recommendation regarding breast cancer screening suggests that all women aged 40 and over undergo a mammogram every 1-2 years, with or without clinical breast examination. In contrast, screening for HIV is not universally recommended.

Consensus Conference Clinical Guidelines:

The National Institutes of Health (NIH) is the medical research agency of the United States. One function of the NIH is to organize conferences to bring together expert scientists and physicians to produce consensus statements on important and controversial topics in medicine. Consensus recommendations are based on publicly available scientific data. These consensus guidelines influence the practice of many physicians throughout the world.

For example, the 2000 NIH Consensus Statement on Adjuvant Therapy for Breast Cancer recommends that the majority of women who have localized breast cancer be treated both with surgery and also with chemotherapy because of the small but statistically significant improvement in survival. [9]

Clinical Preventive Services Guidelines:

Recommendation on Screening for HIV Infection: Clinicians should assess risk factors for HIV infection by obtaining a careful sexual history and inquiring about injection drug use in all patients. Periodic screening for infection with HIV is recommended for all person at increased risk of infection. Screening is recommended for all pregnant women at risk for HIV infection, including all women who live in states, counties, or cities with an increased prevalence of HIV infection. There is insufficient evidence to recommend for or against universal screening among low-risk pregnant women in low-prevalence areas, but recommendations to counsel and offer screening to all pregnant women may be made on other grounds. Screening infant born to high-risk mothers is recommended if the mother's antibody status is not known. All patients should be counseled about effective means to avoid HIV infection. [4]

Read More About the [Institute of Medicine Health Care Quality Initiative](#):

The report *Crossing the Quality Chasm: A New Health System For The 21st Century* was issued by the IOM in 2001. This report calls for comprehensive reform of the health care system to ensure that all patients receive quality, evidence based care.[12]

Committee on Quality of Healthcare in America. (2001). Institute of Medicine. *Crossing the Quality Chasm: A New Health System for the 21st Century*, Washington, DC: National Academy Press. <http://www.nap.edu/catalog/10027.html>.

According to the guide, only those patients who are at risk for HIV need to be regularly tested, such as infants born to high-risk mothers. All recommendations are made by reviewing the available evidence; a test, service, or immunization is recommended only when the data suggests that it will be effective.

Given that health technology assessment has an important effect on policy, it is important to track its use and application, and to ensure that health services delivered to patients are consistent with current professional knowledge. The [Institute of Medicine](#) (IOM) has undertaken a comprehensive effort to assess and improve the quality of health care throughout the United States. The first phase of this initiative began in 1996, and documented serious problems of the quality of health care delivered in the United States, concluding that the burden of harm conveyed by health care quality problems is staggering.[10] For example[11]:

- Only 55% of patients in the US receive care consistent with consensus guidelines.
- The delay between the discovery of more effective forms of treatment and the incorporation of these treatments into routine patient care averages 17 years.
- More than 18,000 Americans die every year as a result of heart attacks because they did not receive preventive medications, even though they were eligible to receive them.
- More Americans are killed every year as a result of medical errors than by breast cancer, AIDS or motor vehicle accidents.

In the second phase of the review, the IOM established a vision to transform the US health care system in order to close the gap between quality care and what exists today in practice. Recommendations include establishing health care systems where decision making is evidence based rather than based on a physician's training and experience, and shifting the view that patient safety is ensured by an individual's responsibility to "do no harm", to one where safety is an inherent property of the health care system as a whole. [12] The third phase of the review, currently ongoing, is focused at implementing these reforms on three levels, the environmental, at the level of health care organizations, and at the interface between clinicians and patients.

As we implement reforms to improve the quality of health systems, it is important to measure whether these reforms

Technology Assessment

actually improve the health of our population. In the next chapter, we will look at various types of health data which are used to assess health status. We will use these measures to compare health status of populations throughout the world.

Chapter 2 Homework

1. Two scientists want to know if a certain drug is effective against high blood pressure. The first scientist wants to give the drug to 1,000 people with high blood pressure and see how many experience lower blood pressure levels. The second wants to give the drug to 500 people with high blood pressure and not give the drug to another 500 people with high blood pressure and see how many people in both groups experience lower blood pressure.

- a. What is the better way to test this drug?
- b. Why is it better to test the drug this way?

2. Find a news report describing a new health technology published in the last year.

- a. Based on this article, summarize which steps in the technology assessment process have been carried out for this technology.
- b. Given this, do you believe that the news report provides a balanced discussion of the potential promise and the potential limitations of this technology?

3. Dr. Maurice Hilleman died recently. A quote from his obituary stated, "I think it can be said without hyperbole that he was a scientist who saved more lives than any other modern scientist."

- a. What was Dr. Hilleman's contribution to medical science?
- b. How many lives per year are saved as a result of his work?
- c. Discuss Dr. Hilleman's work as an example of translational research.

<http://www.upenn.edu/almanac/volumes/v51/n29/obit.html>

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