

Balancing costs and benefits in cancer therapy and prevention

T. D. Szucs¹ & K. J. Dedes²

¹Institute of Social and Preventive Medicine, University of Zurich; ²Division of Gynecology, Department of Obstetrics and Gynecology, University Hospital of Zurich, Zurich, Switzerland

I am fine to sum up with an urgent appeal for adopting this or some uniform system of publishing the statistical records of hospitals. If they would be obtained they would show subscribers how their money was being spent, what amount was really being done with it, or whether the money was doing mischief than good.

Florence Nightingale, 1863

introduction

In an era of increasing cost containment in health care, it has become extremely important to allocate resources as efficiently as possible. This implies that formal health economic considerations are taken into account. One field of increasing importance is that of economic appraisal, which allows quantifying the value for money of medical interventions. This type of research is extremely useful in the field of supportive care for cancer patients. In addition to economic considerations, social, political and ethical issues will also have to be addressed. Finally, the sum of these activities will enable us to make better choices in health care and ensure that sufficient resources are allocated to supportive cancer treatment.

From a clinical economist's point of view, cancer care represents a great challenge. Many issues have evolved over recent years, often yielding more questions than answers. The complexity of the matter, the interdisciplinarity of the approach and the emergence of an increasingly cost conscious health care environment put cancer care in a difficult realm.

Cancer patients have physical, social, spiritual and emotional needs. They may suffer from severe physical symptoms, from social isolation, spiritual abandonment and emotions such as sadness and anxiety, or feelings of deception, helplessness, anger and guilt. In some patients, the disease is rapidly progressing and ultimately they die. Their demanding care evokes intense feelings in health care providers, the more since these incurable patients represent a challenge, which could be condensed under the heading 'the challenge of medical omnipotence'.

The economic burden of cancer is tremendous. It is estimated that approximately 10 million people worldwide suffer from neoplasms. Radice and Redaelli estimate that this figure will increase to 15 million people by the year 2020 [1].

The associated economic burden may well lie in the range of €250–350 billion.

rationale and principles of health economic research

In the past few years the discipline of economic evaluations has experienced an extraordinary boom within the health care sector [2]. Researchers from a wide range of disciplines have developed new techniques to evaluate the impact of clinical care and medical technology [3, 4]. Clinicians, pharmacists, economists, epidemiologists and operations researchers have contributed to the new field of economic evaluations to study how different approaches to patient care influence the resources consumed in clinical medicine [5].

Health economists start with a basic premise that while desires and needs are infinite, resources are limited. They therefore try to find the best way to allocate these resources appropriately, to maximise the overall health of the population. Economic assessment in health care has developed in response to the needs of the administrators, third party payers and politicians to understand the consequences of technological change in health care [6]. In any case, previous decisions about the use of health care technologies were based almost entirely on the clinical safety, efficacy and quality of the products used.

But while numerous economic evaluations have been reported, the quality of the research and, therefore, its validity in decision-making, has been variable [7]. On the other hand, as techniques become more sophisticated, there is a danger that the esoteric nature of the studies may alienate the decision-makers from the analysts [8]. So, decision-makers (as well as scientific journal editors) are increasingly calling for guidance about the principles and methods used, and for help in interpreting studies, judging their quality and determining their applicability to particular settings [9].

the benefits of economic evaluations

Economic evaluations in health care can bring benefits to various target groups. Third party payers will be able to formulate better policies and reach better decisions when allocating funds or negotiating contracts with health care providers. In addition, a better mix of health care services

offered to the insured population can be put together. Health care providers will benefit from economic evaluations by optimising their mix of clinical strategies and choosing from alternative services. Significantly, in the future clinicians themselves will be urged to analyse the economic impact of clinical strategies, in order to counterbalance prioritisation by third party payers and health care administrators. Patients themselves will have to bear more and more of the health care bill, either through co-payments or by risk-adjusted insurance premiums—and their choices will be based on the perceived value of the services offered. So, analyses of patient preferences, which include quality of life assessments, are an ever-growing part of health economic research [10].

The results of economic evaluations can be displayed in the 2x2 matrix of Figure 1, which includes costs and consequences on its axes.

the limitations of economic evaluations

Economic evaluations, however, will not solve all substantive issues. It is vital to be aware that health care cannot be rationed using a simple economic calculation. There are always moral and ethical issues for society to take into consideration. There is also a political danger associated with economic evaluations: they may become the ‘fourth hurdle’ for registration of new products. Regulators may not only review data about a product’s efficacy, safety and quality, but also demand economic efficiency. There are practical problems related to the introduction of a statutory requirement for economic appraisals. They may delay patient access to new technologies, reduce the returns to innovators and push up costs. Analysis of results may be challenged because there are no ‘gold standards’ for conducting economic trials and many regulatory bodies do not (yet) have the expertise to review economic data properly. Nonetheless, many countries are moving towards statutory economic evaluations of new health care products [11, 12].

the major components of an economic evaluation

All economic studies investigate the balance between inputs (the consumption of resources) and outcomes (improvements in the state of health of individuals and/or society).

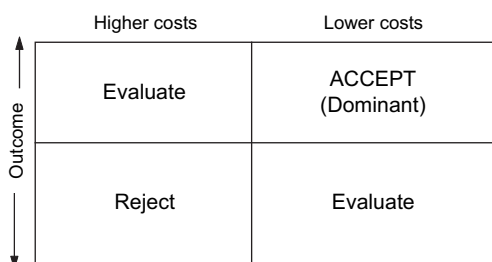


Figure 1. The four possible outcomes of an economic evaluation

inputs (costs)

Although the unit price of a drug or procedure is often a prime factor in decision-making, economic outcomes research provides a more comprehensive interpretation of cost. This is accomplished by determining the overall cost of a given diagnostic and therapeutic process from the initiation of diagnosis until a final outcome is achieved. The various types of costs can be grouped under the following categories: direct medical costs, direct non-medical costs and indirect costs.

direct medical costs. The interpretation of what belongs in each of these categories varies in the economic literature. Direct medical costs are defined as those resources used by the provider in the delivery of medical care. As an example, direct medical costs for a hospital include:

- drugs
- laboratory tests
- medical supplies
- use of diagnostic equipment; e.g. magnetic resonance imaging, computed tomography (CT) scans, X-rays
- medical staff time for personnel such as physicians, nurses, pharmacists, physical therapists, laboratory technicians, etc.
- room and board: the cost of supplies, equipment, and personnel required for routine patient-related services such as food, laundry, and housekeeping

These are examples of costs that can be directly related to the care of patients. Other costs of operating a hospital include plant maintenance and repairs, utilities, telephone, accounting, legal fees, insurance, taxes, real estate costs and interest expenses. In general, most economic studies do not factor general operating costs into the dollar value assigned to the cost of resources expended for a given medicine.

Looking down the list of direct medical expenses, it is easy to see why length of stay is an important cost factor to hospitals, especially when payment is determined by diagnosis related groups. Costs such as room and board are directly tied to the length of stay, regardless of the reason. The cost of laboratory tests, supplies and medical staff time vary with the medical condition being treated, but are multiplied by the length of stay.

Length of stay in hospital settings translates to number of patient visits in managed care settings. Although the specific items included under the category of direct medical costs will be slightly different in managed care organizations, the same principles of cost analysis apply. Drugs that achieve results quickly and predictably not only benefit the patient, but also benefit the provider by reducing the number of patient visits. Every patient visit incurs provider resource costs, which may not be reimbursed by a third-party payer. Interventions that minimize patient visits are clearly a cost saving for the health care organization.

direct non-medical costs. Economic literature generally defines direct non-medical costs as out-of-pocket expenses paid by the patient for items outside the health care sector. This category includes such costs as:

- travel to and from the hospital, clinic, or doctor’s office
- travel and lodging for family members who live elsewhere

- domestic help or home nursing services
- insurance co-payments and premiums
- treatment not covered by third-party payers

Although these costs are generally classified as ‘non-medical’, to the patient they are real and often substantial costs of medical care. What makes them ‘non-medical’ is that they are not costs incurred by the health care provider, and are somewhat difficult to measure. For example:

- A patient’s inability to afford competent follow-up care at home may result in poor compliance with drug therapies and eventual treatment failure. This may lead to additional hospital stays or office visits, which affect the provider’s bottom line.
- A patient’s inability to bear the unreimbursed cost of medications may also lead to poor compliance and costly complications.
- High transportation costs may lead to missed appointments for necessary follow-up visits, which can result in deterioration of a patient’s medical condition and increased treatment costs for the provider.

Even though these costs may not be directly incurred by the provider, they can be used in specific situations by making the provider aware of their potential economic impact. It may also be possible to use these costs to encourage payers (e.g., employers, insurance companies) to discuss the use of a more cost-effective test with the health care provider.

indirect costs. One definition of indirect costs (also called ‘intangible costs’ by some economic analysts) is the overall economic impact of illness on the patient’s life. These include:

- loss of earnings due to temporary, partial, or permanent disability
- unpaid assistance by family members in providing home health care
- loss of income to family members who forfeit paid employment in order to remain at home and care for the patient

Like direct non-medical costs, indirect costs are real to the patient, but abstract to the provider, although they may impact the provider’s direct medical costs. For example, patients who cannot earn income may not be able to pay their bills—including medical bills. Economic hardship may result in poor compliance with drug therapies as patients reduce doses or fail to refill prescriptions in order to save money. The medical provider may have to bear the additional costs of managing complications. Economic hardship may also result in missed follow-up appointments leading to the same types of problems for providers as described previously with direct non-medical costs.

consequences and outcomes. Final states or outcomes can be negative (sometimes referred to as the ‘five D’s’):

- death
- disability (patient is permanently disabled and unable to return to work or school, perform household chores, etc.)
- discomfort (patient is in constant state of moderate to high level of pain)

- dissatisfaction (patient is not satisfied with the course of treatment or services provided)
- disease (patient’s condition is not being controlled resulting in frequent relapses, rehospitalization and expenditure of additional resources).

There are also positive outcomes:

- patient is cured
- patient is able to resume normal functions
- improved or satisfactory quality of life
- patient’s medical condition is successfully managed or stabilized by continued drug therapy.

The use of outcomes research represents an important advance in medical economic analysis because of the relationship between the final state, or result, of diagnosis and therapy and overall cost-effectiveness. If one can demonstrate that a product or intervention will achieve cost-effective positive outcomes, one will increase the chances of diffusing the technology within health care.

important economic concepts

average, marginal and joint costs

Most decisions in health care are not concerned with whether or not a service should be provided, or whether or not a particular procedure should be undertaken, but with how much of the service should be provided. That is, should existing levels of provision be expanded or contracted? For example, should the existing provision of day care for people with mental illness be expanded and, if so, by how much? What family planning services should be made available? How many patients presenting with head injuries should have CT scans? All these decisions require that attention should be focused on marginal costs—that is, the change in total costs resulting from a marginal change in activity.

In the short run there is often an important difference between the marginal costs of an activity and its average cost, where the average cost is defined as the total costs divided by the total number of units of output. Another context in which the distinction between average and marginal costs is important is in relation to duration of hospital stay of inpatients. Many new procedures have reduced the amount of time necessary for a patient to remain in hospital and thereby yield cost savings. When valuing these savings, however, it is important to keep in mind that using average costs/day will generally overstate the savings as the later days of a stay usually cost less than the earlier ones. It is the marginal costs/day that is the relevant measure.

Another problem of cost measurement arises in connection with joint costs. Often a single production process can result in multiple outputs. For example, a single chemical analysis of a blood sample can diagnose the presence of many diseases. How should the cost be allocated to each diagnosis? Similarly, within a hospital setting, there are many common services (like medical records, radiology, operating theatres, laundry, catering and cleaning) that contribute to a number of specialties. Economic evaluation requires some method for allocating the joint costs of these services to individual

programs or procedures. There are several methods that may be used to do this. Most of them use some physical unit of utilization, such as the number of laboratory tests, hours of operating theatre use, or square meters of ward space, to apportion total laboratory, operating theatre and ward cleaning costs.

adjusting for differences in timing: discounting

The current (operating) costs associated with most procedures can be expected to extend over a number of years into the future, but their time profiles may differ. In the case of many preventive procedures, such as treatment for hypertension, costs will be incurred regularly over a number of years. The alternative of no preventive treatment may well incur zero expenditure in the early years but incur the costs of surgery earlier than would otherwise have been the case. Discounting offers a means of standardizing different cost time profiles so that total costs can be compared.

Discounting is based on the assumption that costs incurred in the immediate future are of greater importance than costs incurred in the distant future. This is because earlier access to finance would permit investment at a positive rate of interest, thereby yielding a larger sum in the future (there is an opportunity cost) or because people and society attach more importance to current opportunities than to future ones (positive time preference).

For these reasons, economic evaluation weights costs by a discount rate, according to the year in which they accrue, before adding them up and expressing total costs in present value terms (values in the current year).

In essence, discounting is the reverse application of the more familiar compound interest formula—instead of sums being calculated forwards, they are discounted backwards. Fortunately, the application of discounting does not require close familiarity with the formula as many finance and accounting textbooks include discount tables. These indicate the present values of the pound at different discount rates.

empirical assessment of costs and benefits

Table 1 displays the main types of economic evaluations.

cost-minimisation analyses

Cost-minimisation analysis is concerned with comparing the costs of different treatment modes that produce the same result. For example, this form of analysis could be used to compare the cost of two programs that involve minor surgery for adults. Both have the same outcome in terms of the surgical procedure, but the first program might require the patient to stay overnight at the hospital, and the second might be done through day surgery without requiring hospitalization. Given these two alternatives, the search would be for the least costly treatment. While we might be interested in the extent to which day care surgery shifts costs from the institution to the patient, the main efficiency comparison would be on a cost per surgical procedure basis.

As far as pharmaceuticals are concerned, this type of study is used most frequently when a new drug is introduced into a therapeutic class that includes close competitors and where no measurable therapeutic effect between them has been documented.

When the cost of two interventions is being compared, cost-minimisation analysis often assumes that they lead to the identical health outcome. Studies of this nature should report evidence to support the contention that outcome differences are non-existent or trivial in nature. In most cases, however, the issues are more than that of cost alone. It is rarely the case where two therapies having the same indication produce identical health outcomes in every respect.

cost-effectiveness analyses

Cost-effectiveness studies measure changes in the cost of all relevant treatment alternatives, but measure the differences in outcomes in some natural unit such as actual lives saved, years of lives saved or children immunised. Cost-effectiveness analyses can be applied equally to cases where the outcome is in terms of quality of life. It is useful in comparing alternative therapies that have the same outcome units (e.g., years of life expectancy or of lives saved) but the treatments do not have the same effectiveness (i.e., one drug may lead to greater life expectancy). The measure compared is the cost of therapy divided by the units of effectiveness and, hence, a lower number signifies a more cost-effective outcome.

Table 1. Overview on the main types of pharmacoeconomic evaluations

Type of study	Intervention costs	Consequences	Measurement of consequences	Compares alternatives	Assumes equivalent effectiveness
Cost-benefit analysis	Monetary value of resources consumed	Monetary value of outcomes	Economic	Not necessarily, although comparisons are implicit	No
Cost-effectiveness analysis	Monetary value of resources consumed	Effects on health	Lives saved	Yes	No
Cost-utility analysis	Monetary value of resources consumed	1. Utility of health effects	Cases treated	Yes	No
		2. Indirect costs	Years of life saved		
		3. Subsequent use of resources	Quality-adjusted life-years		
			Economic		
			Economic		

This type of study has the advantage that it does not require the conversion of health outcomes to monetary units and thereby avoids equal benefit and other difficult issues of the valuation of benefits. It has the disadvantage of not permitting comparison across programs that have different endpoints. In other words, a drug whose function is aimed at reducing infant mortality rates cannot be compared with a drug designed to improve functional status of senior citizens. Moreover, it cannot compare outcomes measured in clinical units with quality of life measures.

cost-utility analyses

Cost-utility analysis compares the added costs of therapy with the number of quality-adjusted life years (QALY) gained. The quality adjustment weight is a utility value, which can be measured as part of clinical trials or independently. The advantage of cost-utility analysis is that therapies which produce different or multiple results can be compared.

The QALY, which has been the standard measure of benefit thus far, is arrived at in each case by adjusting the length of time affected through the health outcome by the utility value (on a scale of 0 to 1) of the resulting health status. Many analysts are more comfortable with this measure of the consequence of medical care than with the use of money as the measure of benefits. A recent addition to the field is the healthy-years equivalents which attempt to overcome problems associated with the QALY methodology. Table 2 gives an overview of utility values in the case of breast cancer.

Cost-utility analysis is an improvement over cost-effectiveness analysis because it can measure the effects of multiple outcomes (such as the impact of drugs on both morbidity and mortality or the impact on both pain and physical functional status).

cost-benefit analyses

As applied to health care, cost-benefit analysis measures all costs and benefits of competing therapies in terms of monetary units. Generally, a ratio of the discounted value of benefits to costs (the present value of both) is calculated for each competing therapy. The ratios for each of the competing therapies and for competing programs (e.g., intensive care unit versus new diagnostic equipment) can be readily compared.

Table 2. Utility values exemplified for the case of metastasizing breast cancer [23]

Health state	Utility
Partial response	0.81
Stable disease	0.62
Before commencement of second line treatment	0.59
Partial response plus severe neuropathy	0.53
Progressive disease	0.41
Sepsis	0.20
Terminal disease	0.16

Rx, .

Cost-benefit analysis has the shortcoming of requiring the assignment of a dollar value to life and to health improvements including quality of life variables. This presents equal benefit issues as well as substantial measurement problems. For these reasons cost-benefit analysis has not been widely used in recent years for evaluating health technologies.

using economic analyses in decision making

Just conducting economic research is often not enough. What has to be done is to increase the impact of such evaluations. A lot of economic data has already been compiled but is not being used properly. So the future lies also in using results and increasing the impact of those evaluations [13]. One means is, for example, to involve decision makers in the planning of such studies. In the past manufacturers have produced data and tried to convince decision makers, instead of working together with decision makers beforehand. It should always be noted that economic analysis and economic data will only represent one part of the information required for the decision process. The next step is to make decision makers aware of the usefulness of an economic evaluation.

The next point is to make the study aware in the community by all means of publication and communication, preferably through the channels that reach decision makers. This means that methodologies have to be reviewed in terms of their credibility, financial costs and the time to complete. Classifications such as those used in the Cochrane Collaboration, for example, may also be suitable for analyzing and rating the sources for economic evaluations [14]. Table 3 lists a rank order of methodologies for assessing the credibility. In those cases where economic studies cannot be combined with randomized controlled studies, modelling techniques have to be employed. However, good modeling practice should be envisaged [15]. Checklists have been developed in order to facilitate the appraisal of the quality of economic analyses and assist in minimizing possible bias [16, 17]. These criteria are also being increasingly used in the peer review process by many biomedical journals [18] and discussed accordingly [19]. In many countries, such as Canada and Australia, economic appraisal is a prerequisite for acceptance of a new pharmaceutical product to be considered reimbursable [20, 21].

Another important question is whether preventive health care is a more economically attractive investment than curative technologies. Recently, Cohen et al. [22] analyzed the Tufts New England Medical Center Cost-Effectiveness Analysis Registry (www.tufts-nemc.org/cearegistry). They discovered that the distributions of cost-effectiveness ratios for preventive measures and treatments are very similar. Figure 2 shows the distribution of cost-effectiveness ratios for preventive measures and treatments for existing conditions.

challenges for the future

Further health economic studies will have to fulfil certain needs. These will likely be (i) the establishment of the drugs

Table 3. League table for various medical interventions in oncology

Intervention	Costs/life year US\$	Author
Surgery in 70-year-old men with a new diagnosis of prostate cancer, compared with watchful waiting	Increases costs and worsens health	Basu, 2005 [24]
Routine cost-effectiveness analyses monitoring of colon cancer	31 000–6 600 000	Kievit, 1990 [25]
Allogeneous bone marrow transplantation for relapse of M. Hodgkin	421 000	Desch, 1992 [26]
Bone marrow transplant and high dose (versus standard dose) chemotherapy for breast cancer	129 179	Hillner, 1992 [27]
Bevacizumab in the first-line treatment of metastatic colorectal cancer versus irinotecan plus 5-fluorouracil	124 000	Tappenden, 2007 [28]
Allogeneous bone marrow transplantation in metastatic breast cancer	115 800	Hillner, 1992 [27]
Chemotherapy of acute non-lymphocytic leukemia	80 300	Welch, 1989 [29]
Quality-controlled mammography screening in 40-year-old women	73 018	Neeser, 2007 [30]
Adjuvant CMF in breast cancer, 75-year-old women	44 000	Desch, 1993 [30]
Trastuzumab in the adjuvant treatment of early breast cancer	27 000	Dedes, 2007 [31]
Intensive tobacco use prevention program in 7th and 8th graders	23 000	Venditti, 2003 [32]
Post-surgical chemotherapy for women with breast cancer age 60	22 105	Hillner, 1991 [33]
Post-surgical chemotherapy for premenopausal women with breast cancer	18 107	Hillner, 1991 [33]
Interferon alpha-2b in hairy cell leukemia	13 800	Ozer, 1989 [34]
Taxol as first-line chemotherapy of ovarian cancer (six European countries)	6400–11 400	Berger, 1989 [35]
Adjuvant CMF in breast cancer, 45-year-old women	4900	Hillner, 1992 [27]
Tamoxifen in advanced breast cancer	810	Rees, 1985 [36]
One-time colonoscopy screening for colorectal cancer in men 60–64 years of age	Cost-saving	Ness, 2000 [37]

CMF, cyclophosphamide, methotrexate, fluorouracil.

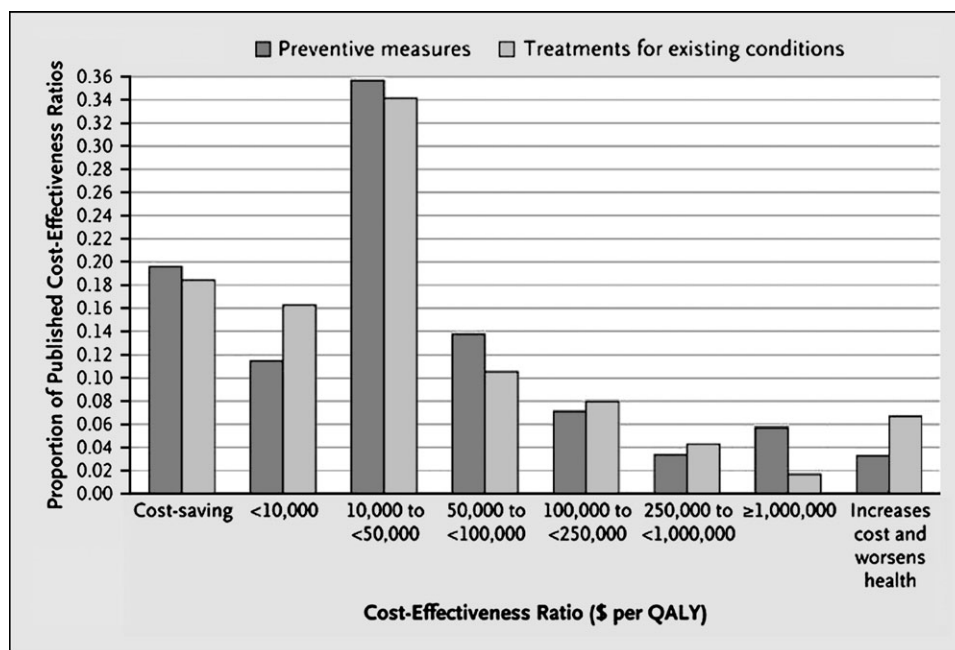


Figure 2. Distribution of cost-effectiveness ratios for preventive measures and treatments for existing conditions (data are from the Tufts–New England Medical Center Cost-Effectiveness Registry). QALY denotes quality-adjusted life-year.

effectiveness under real (every day) conditions as opposed to clinical trial conditions, (ii) the determination of the real value of production losses and their proper measurement, (iii) improved conditions for implementing new programmes and (iv) cost estimates for more ambitious programmes. Furthermore, the adaptation of economic studies across

countries will not be an easy task. Problem areas in this respect may be the choice of the perspective of the economic study, local practice patterns and the customer structure for drug purchasing decisions. Also, patient preferences as well as the different sociodemographic structure, price levels and effectiveness will have to be taken into consideration.

disclosures

No significant relationships

references

- Radice D, Redaelli A. Breast cancer management: quality-of-life and cost considerations. *Pharmacoeconomics* 2003; 21: 383–396.
- Elixhauser A. (eds.). Health care cost-benefit and cost-effectiveness analysis (CBA/CEA). From 1979 to 1990. a bibliography. *Medical Care* 1993; 31 (Suppl): JS1–JS149.
- Bloom BS. Medical management and managing medical care: The dilemma of evaluating new technology. *Am Heart J* 1990; 119: 754–760.
- Banta HD. Health Care Technology and its Assessment. Oxford, UK: Oxford Medical Publications 1993.
- Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in Health and Medicine. Oxford, UK: Oxford University Press 1996.
- Blumenschein K, Johannesson M. Economic evaluation in healthcare: a brief history and future directions. *Pharmacoeconomics* 1996; 10: 114–122.
- Udvarhelyi IS, Colditz G, Rai A. Cost-effectiveness and cost-benefit analyses in the medical literature: are the methods being used correctly? *Ann Intern Med* 1992; 116: 238–244.
- Davies L, Coyle D, Drummond M. Current status of economic appraisal of health technology in the European Community: report of the network. *Soc Sci Med* 1994; 38: 1601–1607.
- Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996; 313: 275–283.
- Kassirer JP. Incorporating patients' preferences into medical decisions [editorial]. *N Engl J Med* 1994; 330: 1895–1896.
- Ministry of Health (Ontario). Ontario Guidelines for Economic Analysis of Pharmaceutical Products. Toronto, Canada: Ministry of Health 1994.
- Department of Health and Association of the British Pharmaceutical Industry. Guidelines for the Economic Evaluation Pharmaceutical. London, UK: Department of Health 1994.
- Coyle D. Increasing the impact of economic evaluations on health-care decision making. Discussion Paper 108, York 1993.
- Chalmers-I, Haynes B. Reporting, updating, and correcting systematic reviews of the effects of health care. *BMJ* 1994; 309: 862–865.
- Buxton MJ, Drummond MF, Hout BA et al. Modelling in economic evaluation. A first and last resort? *Health Economics* 1997; 6: 217–227.
- Drummond MF, Stoddard GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford, UK: Oxford Medical Publications 1987.
- Task Force on Principles for Economic Analysis of Health Care Principles. Economic analysis of health care technology. A report on principles. *Ann Intern Med* 1995; 123: 61–70.
- Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996; 313: 275–283.
- Kassirer JP, Angell M. The journal's policy on cost effectiveness analysis. *N Engl J Med* 1994; 331: 669–670.
- Commonwealth Department of Health, Housing and Community Services. Guidelines for the pharmaceutical industry on the preparation of submissions to the pharmaceutical benefits advisory committee. Canberra: Australian Government Publishing Service 1992.
- Canadian Coordinating Office of Health Technology Assessment (CCOHTA). Guidelines for the economic evaluation of pharmaceutical. Ottawa, Canada: CCOHTA 1994 www.ccohta.com.
- Cohen JT, Neumann PJ, Weinstein MC. Does preventive care save money? Health economics and the presidential candidates. *N Engl J Med* 2008; 358: 661–663.
- Hillner BE. Role of decision analysis in relation to clinical trials and a US perspective of the Battelle model. *Pharmacoeconomics* 1996; 9 (Suppl 2): 30–36-6 Review.
- Basu A, Meltzer D. Implications of spillover effects within the family for medical cost-effectiveness analysis. *J Health Econ* 2005; 24: 751–773.
- Kievit J, van de Velde CJH. Utility and cost of carcinoembryonic antigen monitoring in colon cancer follow-up evaluation. A Markov analysis. *Cancer* 1990; 65: 2580–2587.
- Desch CE, Lasala MR, Smith TJ et al. The optimal timing of autologous bone marrow transplantation in Hodgkin's disease patients following a chemotherapy relapse. *J Clin Oncol* 1992; 10: 200–209.
- Hillner BE, Smith TJ, Desche CE. Efficacy and cost-effectiveness of autologous bone marrow transplantation in metastatic breast cancer. *J Am Med Assoc* 1992; 267: 2055–2061.
- Tappenden P, Jones R, Paisley S, Carroll C. The cost-effectiveness of bevacizumab in the first-line treatment of metastatic colorectal cancer in England and Wales. *Eur J Cancer* 2007; 43: 2487–2494.
- Welch HG, Larson EB. Cost-effectiveness of bone marrow transplantation in acute nonlymphocytic leukemia. *N Engl J Med* 1989; 321: 807–812.
- Neeser K, Szucs T, Bulliard JL et al. Cost-effectiveness analysis of a quality-controlled mammography screening program from the Swiss statutory health-care perspective: quantitative assessment of the most influential factors. *Value Health* 2007; 10: 42–53.
- Dedes KJ, Szucs TD, Imesch P et al. Cost-effectiveness of trastuzumab in the adjuvant treatment of early breast cancer: a model-based analysis of the HERA and FinHer trial. *Ann Oncol* 2007; 18: 1493–1499.
- Venditti LN, Venditti CP, Berry GT et al. Newborn screening by tandem mass spectrometry for medium-chain acyl-CoA dehydrogenase deficiency: a cost-effectiveness analysis. *Pediatrics* 2003; 112: 1005–1015.
- Hillner BE, Smith TJ. Efficacy and cost-effectiveness adjuvant chemotherapy in woman with node-negative breast cancer. *N Engl J Med* 1991; 324: 160–168.
- Ozer H, Golomb HM, Zimmerman H et al. Cost-benefit analysis of interferon alpha 2b in treatment of hairy cell leukemia. *J Natl Cancer Inst* 1989; 81: 594–602.
- Berger K, Szucs T. Cost-effectiveness analysis of paclitaxel and cisplatin versus cyclophosphamide and cisplatin as first-line therapy in advanced ovarian cancer. A European perspective. *Eur J Cancer* 1998; 34: 1894–1901.
- Rees GJG. Cost-effectiveness in oncology. *Lancet* 1985; 2: 1405–1408.
- Ness RM, Holmes AM, Klein R, Dittus R. Cost-utility of one-time colonoscopic screening for colorectal cancer at various ages. *Am J Gastroenterol* 2000; 95: 1800–1811.