Research Techniques Made Simple: Cost-Effectiveness Analysis

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Cost-effectiveness analysis (CEA) is a research method used to determine the clinical benefit-to-cost ratio of a given intervention. CEA offers a standardized means of comparing cost-effectiveness among interventions. Changes in quality-adjusted life-years, disability-adjusted life-years, or survival and mortality are some of the common clinical benefit measures incorporated into CEA. Because accounting for all associated costs and benefits of an intervention is complex and potentially introduces uncertainty into the analysis, sensitivity analyses can be performed to test the analytic model under varying conditions. CEA informs the identification of high-value clinical practices and can be used to evaluate preventative, diagnostic, and therapeutic interventions in dermatology.

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Description: This article, designed for dermatologists, residents, fellows, and related healthcare providers, seeks to reduce the growing divide between dermatology clinical practice and the basic science/current research methodologies on which many diagnostic and therapeutic advances are built.

Objectives: At the conclusion of this activity, learners should be better able to:
- Recognize the newest techniques in biomedical research.
- Describe how these techniques can be utilized and their limitations.
- Describe the potential impact of these techniques.

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WHAT IS COST-EFFECTIVENESS ANALYSIS?

Cost-effectiveness analysis (CEA) is a research method that characterizes the costs of interventions relative to the amount of benefit that they yield. CEA provides a standardized means of comparing interventions to identify those that provide maximal clinical effect per incremental unit of cost. CEA can be applied to preventive, diagnostic, and therapeutic interventions. Outcomes captured by such analyses can include mortality benefit, symptom reduction, or improved quality of life after a treatment or procedure. CEA is one type of economic analysis used in health services research; other related but separate concepts are outlined in Table 1.

Given the interest in delivering high-value care across all clinical specialties including dermatology, research identifying clinical practices that deliver a high level of

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Abbreviations: CEA, cost-effectiveness analysis; DALY, disability-adjusted life-year; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year

SUMMARY POINTS

What is cost-effectiveness analysis?

Cost-effectiveness analysis (CEA) is a research method used to determine the clinical benefit-to-cost ratio of interventions. CEA offers a standardized means of comparing cost effectiveness among interventions.

Changes in quality-adjusted life-years (QALYs), disability-adjusted life-years (DALYs), or survival and mortality are some of the common outcome measures of clinical benefit incorporated into CEA.

CEA can be used to evaluate screening, preventative, diagnostic, and therapeutic interventions.

Limitations of cost-effectiveness analysis

Accounting for all associated costs and benefits of an intervention is complex, potentially introducing uncertainty into the analysis. Sensitivity analyses can be performed to test the analytic model under varying conditions.

There remains no universally accepted standard for cost-effectiveness thresholds.

Table 1. Comparison of concepts in health economics analysis

Concept	Definition
Cost analysis	Calculation of the costs associated with an intervention
Cost-benefit analysis	Characterization of the cost of an intervention relative to the monetary benefit of its outcome
Cost-effectiveness analysis	Characterization of the cost of an intervention relative to the clinical benefits of the outcome, measured in nonmonetary values
Comparative effectiveness research[1]	A field of research that aims to discriminate among clinical interventions according to their clinical effectiveness, cost effectiveness, and appropriateness

[1]Nambudiri and Qureshi, 2013.

effectiveness at a relatively lower cost can be valuable in guiding policy on allocation of health care resources. It is thus increasingly relevant for dermatologists to understand CEA and demonstrate cost-effectiveness in current practice.

METHODS IN COST-EFFECTIVENESS ANALYSIS

Core elements of cost-effectiveness analysis include identifying clinical interventions, accounting for all associated costs, and defining outcome measures for analysis. The Panel on Cost-Effectiveness in Health and Medicine provides recommendations on variables that should be included in cost and outcome definitions used in CEA (Sanders et al., 2016). Cost calculations should include not only the price of administering an intervention but also costs associated with facility and staff resources, intervention adverse effects, and indirect costs of patient suffering and lost productivity, among others.

Table 2 outlines various outcome measures used in CEA. The most commonly used outcome measures are the disability-adjusted life-year (DALY) and quality-adjusted life-year (QALY). For both DALYs and QALYs, a value of 1 is assigned to a single year lived with perfect health. To determine the DALYs associated with a condition, a disability weight is assigned based on the level of impairment caused by the condition, with larger disability weights correlated with greater impairments to health (Jamison et al., 2006). The disability weight is then subtracted from 1 to determine the DALY. QALYs are calculated in a similar fashion but incorporate quality of life changes into the measurement. Standardized quality of life surveys such as the EuroQol five dimensions questionnaire (EQ-5D) are commonly used to derive QALY values (Prieto and Sacristán, 2003). DALY and QALY determinations are informed by standardized disease severity, symptom, and quality of life measurements and in many cases are preferable markers of health outcomes over simply counting life-years prolonged (Jamison et al., 2006). Dermatology-related instruments that have been developed and validated include the Dermatology Life Quality Index (DLQI), Children's Dermatology Life Quality Index, Psoriasis Area and Severity Index (PASI), SCOring Atopic Dermatitis (SCORAD), and Functional Assessment of Cancer Therapy Melanoma (FACT-M), among others.

Decision analysis models are used to analyze large volumes of patient outcomes in CEA. A decision tree, which allows visualization of the different clinical pathways being compared and their possible outcomes, is an example of a simple decision analysis model (Figure 1). Probabilities of an intervention's success or failure are estimated from existing literature on efficacy, and the decision tree allows for the incorporation of outcomes such as cost and QALYs. However, the decision tree is less well adapted to handling recurrent conditions and longer-term outcomes. The Markov model, an iterative model that accommodates transitions among various disease states, can be better suited for representing conditions that recur, evolve, and progress over time (Sonnenberg and Beck, 1993).

Table 2. Definitions of selected outcome measures used in CEA[1]

Outcome measure	Definition
Mortality (deaths averted)	The number of deaths prevented by an intervention
Life-years gained/lost	The remaining life expectancy at the time of an averted death, weighted in favor of younger persons.
Disability-adjusted life-years gained/lost	A unit of the amount of health lost because of a condition, taking into account the burden of morbidity associated with the condition
Quality-adjusted life-years gained/lost	A unit of the years of life saved and adjusted for health-related quality of life with that condition

[1]Adapted from Jamison et al., 2006.

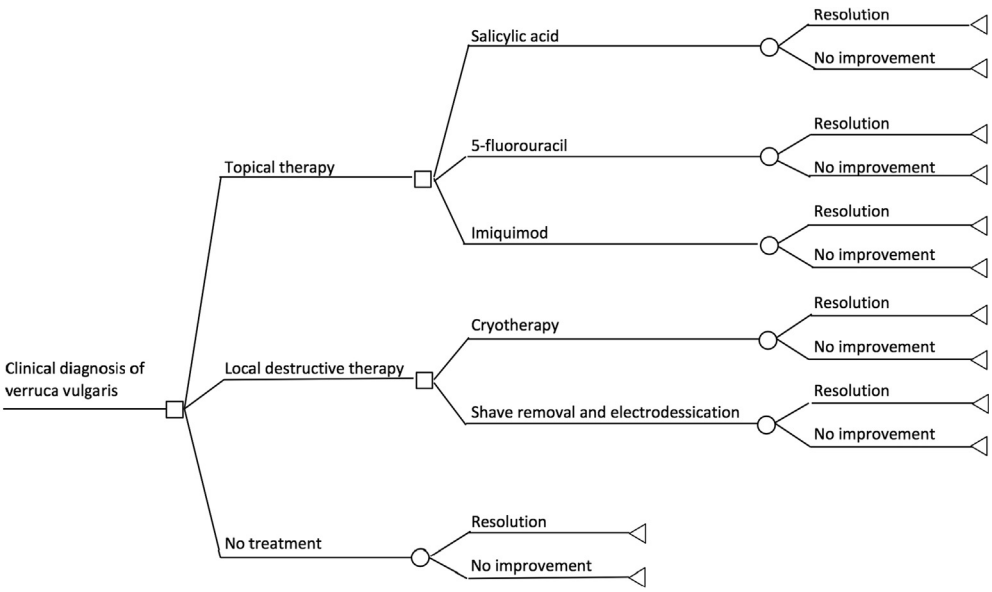

Figure 1. Representative decision tree of management pathways for verruca vulgaris. The figure illustrates an example of a clinical decision tree for the management of a common dermatologic condition using select strategies currently used in clinical practice. It does not exhaustively show all therapeutic options.

There is inherent uncertainty in estimations of the inputs and outputs in CEA. Sensitivity analyses are incorporated into CEA to test decision analysis models under varying conditions. A sensitivity analysis might include testing outcomes after changing the estimate of a treatment cost or under assumptions of lesser treatment efficacy than reported in the literature.

The calculated incremental cost-effectiveness ratio (ICER) allows for comparison of cost-effectiveness between interventions. The basic formula for the ICER of an intervention X relative to a comparison intervention Y (e.g., the current standard of care, the control treatment, or no intervention if there is no current available therapy) is as follows:

$$ICER = \frac{(cost\ of\ intervention\ X - cost\ of\ comparison\ intervention\ Y)}{(effect\ of\ intervention\ X - effect\ of\ comparison\ intervention\ Y)}$$

ICER is commonly reported in units of $/DALY or $/QALY. Historically, a commonly used threshold below which an intervention is considered *cost effective* has been $50,000/QALY, but recommended cost-effectiveness thresholds vary widely. For instance, the National Institute for Health and Care Excellence in the United Kingdom uses a threshold range of £20,000–£30,000/QALY (approximately $25,351–$38,026/QALY) (McCabe et al., 2008), whereas the World Health Organization recommends thresholds of less than three times a nation's per capita gross domestic product/QALY (Marseille et al., 2015). The threshold for cost effectiveness remains an area of active discussion in health economics research (Neumann et al., 2014).

CEA IN DERMATOLOGY: PREVENTION

A large-scale retrospective CEA published by Gordon et al. in the *Journal of Investigative Dermatology* in 2009 investigated the cost effectiveness of routine sunscreen use for skin cancer prevention versus usual practice (i.e., discretionary sunscreen use) in Australia. Program participants were supplied with sunscreen to use over the course of the study.

The net societal costs per person—which included total costs incurred by patients (i.e., time to attend provider visits), providers (i.e., provider salaries, facility costs, sunscreen costs), and the Australian government, the predominant payer in the Australian health care system—over the 5-year period were $405 and $275 for the daily sunscreen treatment intervention and usual practice groups, respectively. However, the authors noted that the intervention represented a net savings for the Australian government because of decreased need for treatment of squamous cell carcinoma, basal cell carcinoma, and actinic keratosis in the intervention group, yielding a total savings of $88,203 over the 5-year period. At an investment of just $0.74 per person per year, the authors concluded that the intervention was favorably cost effective for Australia compared with other public health prevention interventions.

Variables examined in the sensitivity analyses included misdiagnosis costs, costs associated with sunscreen purchase, costs associated with medical visits (which showed wide variation), and proportion of actinic keratoses treated, for which there is no single standardized clinical pathway (Table 3). The intervention consistently offered net cost savings to the government across the sensitivity analyses; however, variation in medical costs and in the proportion of actinic keratoses treated had significant effects on estimated cost-effectiveness ratios (Table 3), illustrating how calculated cost-effectiveness ratios can change by varying assumptions and inputs in these analyses. Although the generalizability of the study to other countries remains to be seen, this article provides an example of a CEA with direct impact on dermatology and skin cancer prevention.

In another recent CEA related to dermatology, a study published in *JAMA Pediatrics* examined the cost effectiveness of six different daily total-body moisturizer treatments used as a means of prevention for the first 6 months of life among newborns at high risk for developing atopic dermatitis (Xu et al., 2016). Unlike the aforementioned skin cancer

Table 3. Sensitivity analyses of the incremental cost-effectiveness ratio of population-wide routine sunscreen use under varying conditions

		Incremental cost-effectiveness ratio (mean per person)
Base analysis		3.72
Costs involved in skin cancer misdiagnoses (positive predictive value)	0.60	3.62
	0.80[1]	3.79
Medical costs ($)	Low	3.81
	High[2]	0.33
Time to visit a GP ($)	Low	3.79
	High	3.70
Time to apply sunscreen ($)	Low	3.77
	High	3.66
Sunscreen purchases ($)	Low	3.52
	High	3.93
Out-of-pockets for GP visit ($)	Low	3.77
	High	3.70
Proportion of AKs treated	0%	6.31
	25%	5.02
	100%	1.15

Abbreviations: AKs, actinic keratosis; GP, general practitioner.
[1]Includes the scenario of higher accuracy and less resource use in experienced or specialist doctors.
[2]Includes the scenario of higher costs of skin cancers treated in hospitals.
From Gordon et al., 2009, reprinted with permission.

study, which used observed clinical outcomes from a randomized controlled trial as the effect measure, this CEA adapted cost and effect findings from a previous report that showed the relative risk reduction of atopic dermatitis after moisturizer treatment among newborns (Simpson et al., 2014). Sensitivity analyses examined treatment effects ranging from 28%–90% relative risk reductions. The cost effectiveness of moisturizer treatments ranged from $353/QALY to $8,386/QALY for the least and most expensive moisturizers included in the study, both well below commonly accepted thresholds for cost effectiveness in the United States.

The authors noted that moisturizers, despite evidence of clinical cost- effectiveness, are not included in insurance coverage and thus are frequently out-of-pocket expenses that pose economic burdens for patients with atopic dermatitis. The two preventive studies cited here highlight cost-effective interventions for which intervention costs are most often borne by patients, despite the benefits and cost savings accruing to government and insurance payers. This discordance represents a challenging dilemma in cost-effectiveness research but potentially also an opportunity for advocacy in expanding payment coverage for these beneficial, evidence-based, cost-effective interventions in disease prevention.

CEA IN DERMATOLOGY: THERAPEUTICS

Given the range of treatment options that exist for dermatologic diseases and concerns of escalating costs associated with novel therapies, CEA is increasingly conducted to evaluate emerging treatments. For example, in an analysis of trametinib plus dabrafenib in the treatment of BRAF V600-mutated melanoma in Switzerland, the authors found that based on current pricing, trametinib plus dabrafenib had an ICER of 385,603 Swiss francs/QALY (approximately $379,624/QALY), making it a less cost-effective treatment than vemurafenib monotherapy, despite potentially being more clinically effective (Matter-Walstra et al., 2015). It is

MULTIPLE CHOICE QUESTIONS

1. This unit of cost effectiveness is defined as

$$\frac{(\textit{cost of intervention X} - \textit{cost of comparison intervention Y})}{(\textit{effect of intervention X} - \textit{effect of comparison intervention Y})}$$

   A. Cost-benefit ratio
   B. Quality-adjusted life-year
   C. Incremental cost-effectiveness ratio
   D. Average cost effectiveness

2. What type of analysis is performed to simulate real-world uncertainty in the parameters of the cost-effectiveness analysis and test assumptions under varying conditions?
   A. Cost-benefit analysis
   B. Sensitivity analysis
   C. Comparative effectiveness analysis
   D. Chi-square analysis

3. This type of model can be useful in cost-effectiveness analysis for simulating the complex course of chronic disease or conditions in which there is transition back and forth between disease states.
   A. Decision tree analysis
   B. Logistic regression model
   C. Cox proportional hazards model
   D. Markov model

4. Which of the following is a commonly used threshold for valuing a single quality-adjusted life-year (QALY) in cost-effectiveness analysis?
   A. $500/QALY
   B. $5,000/QALY
   C. $50,000/QALY
   D. $500,000/QALY

5. Which of the following costs should be factored in as part of a cost-effectiveness analysis for a newly developed pharmaceutical treatment?
   A. Retail price of the drug
   B. Physician time necessary to administer the drug to patients
   C. Patient time out of work to recover from adverse effects of the drug
   D. All of the above

important to appreciate, however, that because treatment prices change with time, so too may cost-effectiveness calculations. Thus, updating historical analyses to reflect current costs may prove informative.

CEA has also been used to identify cost-effective interventions in current practice. In a CEA of topical regimens for mild to moderate localized psoriasis, a Markov model was constructed to simulate clinical pathways for psoriasis management (Sawyer et al., 2013). Use of the iterative Markov model in this study illustrates its value in analyses of chronic and frequently relapsing diseases such as psoriasis. The authors concluded that the most cost-effective first-line therapy for psoriasis of the body was twice-daily potent corticosteroids, with an ICER of £20,000/QALY (approximately $25,351/QALY), whereas very potent corticosteroids were the most cost-effective treatment for scalp psoriasis.

As these examples show, CEA identifies interventions within dermatology that confer benefits to patients, provide cost savings for health systems, and inform policy decisions. CEA of both preventive and therapeutic measures brings into greater focus the relative advantages and disadvantages of implementing various interventions from both clinical and cost perspectives.

FUTURE DIRECTIONS IN CEA AND DERMATOLOGY

Decreases in melanoma mortality after a population-based melanoma screening program in Schleswig-Holstein, Germany (Breitbart et al., 2012) have led to renewed interest in evaluating whether similar comprehensive screening programs could be implemented cost-effectively in other countries. CEA is increasingly included in clinical trials to enable demonstration of favorable cost-effectiveness profiles in addition to evidence of therapeutic value and has been applied to the analysis of care models themselves, such as investigations of the cost-effectiveness of teledermatology programs. Clinicians and investigators alike should be familiar with CEA methodology and the many ways in which CEA can be used in the evaluation of preventive, diagnostic, and therapeutic measures for skin diseases. Understanding CEA research techniques can aid physicians and researchers as they design clinical trials, engage in policy-related advocacy, and make clinical decisions affecting the care of individuals with dermatologic diseases.

CONFLICT OF INTEREST

The authors state no conflict of interest.

AUTHOR CONTRIBUTIONS

CS is a medical student/trainee and VEN is faculty. Both authors were responsible for manuscript conception, design, drafting, and critically revising content. Both authors gave final approval of the version to be published and agree to be accountable for all aspects of the work.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to this paper. Teaching slides are available as supplementary material.

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