Discussion Paper No. 39

November 2026

Cost Effectiveness Thresholds: Ethical Considerations and Practical Reality

Initial Findings from an Integrative Review



INNOVAL HC
Institute for Innovation & Valuation in Health Care

Michael Schlander, Ramon Schaefer,
Stacey Hickson, Danielle Rollmann, Christoph Glaetzer,
Maarten Postma, and Søren Holm

Cost Effectiveness Thresholds: Ethical Considerations and Practical Reality

Initial Findings from an Integrative Review

ISBN 978-3-941609-38-9

INNOVAL HC

Institute for Innovation & Valuation in Health Care

Institut für Innovation & Evaluation im Gesundheitswesen

Discussion Paper

No. 39

Cost Effectiveness Thresholds: Are They Helpful or Do They Mislead Policy-Makers?

Initial Findings from an Integrative Review

Michael Schlander, Ramon Schaefer,
Stacey Hickson, Danielle Rollmann, Christoph Glaetzer,
Maarten Postma, and Søren Holm

November 2026

INNOVAL HC

IV

About the Authors

Michael Schlander[a-d], Ramon Schaefer[a],
Stacey Hickson[e], Danielle Rollmann[e], Christoph Glaetzer[e],
Maarten Postma[f-i], Søren Holm[k,l]

[a]Institute for Innovation & Valuation in Health Care, Wiesbaden, Germany,
[b]University of Heidelberg, Alfred Weber Institute for Economics, Heidelberg, Germany,
[c]University of Heidelberg, Mannheim Medical Faculty, Heidelberg, Germany
[d]German Cancer Research Center / Deutsches Krebsforschungszentrum (DKFZ), former Division of Health Economics, Heidelberg, Germany
[e]Johnson & Johnson Innovative Medicine, Raritan, NJ
[f]University of Groningen, Faculty of Medical Science, University Medical Center, Groningen, The Netherlands
[g]University of Groningen, Faculty of Economics & Business, Department of Economics, Econometrics & Finance, Groningen, The Netherlands
[h]University of Padjadjaran, Center of Excellence for Pharmaceutical Care Innovation, Bandung, Indonesia
[i]Airlangga University, Faucly of Medicine, Division of Pharmacology & Therapy, Surabaya, Indonesia
[k]University of Manchester, Centre for Social Ethics and Policy, Manchester, Great Britain
[l]University of Oslo, Centre for Medical Ethics, HELSAM, Oslo, Norway

Correspondence:

Professor Michael Schlander, MD, PhD, MBA
Institute for Innovation & Valuation in Health Care (InnoVal[HC])
An der Ringkirche 4, D-65197 Wiesbaden / Germany

Phone: +49 (0) 611 4080 789 12; Facsimile: +49 (0) 611 4080 789 99
E-Mail: michael.schlander@innoval-hc.com

ISBN 978-3-941609-38-9

IV

Table of Contents

Summary 4

Introduction 7

Problem Statement 11

Research Objective 12

Methods 13

Key Observations & Discussion 18

Conclusions 63

Afterword 69

References 70

Appendix 132

Glossary (Acronyms) 136

Acknowledgements

The first phase of the InnoVal[HC] project on cost effectiveness thresholds ("CETs") was supported by Johnson & Johnson Innovative Medicine, Raritan, New Jersey, under an unrestricted educational grant policy. Stacey Hickson, Danielle Rollmann and Christoph Glaetzer are employees of Johnson & Johnson Innovative Medicine. The views and opinions expressed herein are strictly those of the authors and do not represent the views of their employer. Any errors, deficiencies, or problems in this paper are the sole responsibility of the authors.

IV

Contents in Detail

Summary 6

Introduction 9

Problem Statement 13

Research Objective 14

Methods 15

Approach 15

Search strategy 16

Analysis 17

Key Observations & Discussion 20

How CETs have been used 20

The Oregon Health Plan (OHP) experience 21

Thresholds in countries using CETs 24

Australia 24

Canada 25

United Kingdom (England and Wales) 26

Rejection of CE approaches to HTA 29

Methodological challenges: The plausible size of a CET 31

Ethical considerations: The "rule of rescue," social preferences, measurement challenges 36

Critical assumptions 39

Social preferences other than "efficiency" 43

Some further anomalies (reflective equilibrium issues) 46

Treating persons: Equality of QALYs or equality of patients? 48

IV

The empirical relevance of co-existing conditions 50
CETs and the ICER as ratios 53
Rare diseases and orphan medicinal products (OMPs) 53
Budget impact and "affordability" 57
Real world observations 59
Delayed access due to prolonged HTA processes 60
Threshold adjustments 61
Alternative access programs for non-CE treatments have been attempted 63

Conclusions **65**
Afterword **71**
References **72**
Appendix **134**
Glossary (Acronyms) **138**

Figures & Tables

Fig. 1: Number of published CEA studies from 1976–2024 10
Tab. 1: International milestones of applied health economics 23
Tab. 2: Major iterations of England´s approach since 1999 28

Fig. A1: PRISMA flow diagram textbook search 134
Fig. A2: PRISMA flow diagram database search including seminal/defining papers and gray literature 135
Tab. A1: Search strings for electronic databases 136
Tab. A2: Articles assessed for eligibility criteria 137

IV

Summary

Health Technology Assessments (HTAs) typically rest primarily on one or two pillars. An assessment of comparative clinical effectiveness may be followed by a formal comparative economic evaluation, which usually takes the form of a cost effectiveness analysis (CEA) with life years gained (LYGs) or, most often, quality-adjusted life years (QALYs) gained as a putatively universal and comprehensive measure of benefit ("*effectiveness*"). To be useful, CEAs require a benchmark or "*cut-off*" level, separating cost effective from not cost effective health care programs.

The use as well as the value of these "*cost effectiveness thresholds*" (CETs) is controversial and varies across jurisdictions. Given the far-reaching consequences for the coverage of interventions and therefore patients' access to treatment in many health systems, a project has been initiated to systematically review and analyze the theoretical underpinnings of, the practical experience with, and the lessons learnt from the use of CETs to inform health care priority setting, in particular in the context of HTAs, the main objective being to bring about a critical yet balanced perspective on the roles and limitations of CETs by means of an integrative review project.

The present report offers, in the form of a narrative review, an initial overview of major insights and tentative conclusions emerging from the project, drawing on experience and debate in the United States (*Oregon Health Plan*, OHP), Australia (*Pharmaceutical Benefits Advisory Committee*, PBAC), Canada (*Canada's Drug Agency*, CDA-AMC), and the United Kingdom (*National Institute for Health and Care Excellence*, NICE).



Following a brief summary of the early adoption of CEA and CETs in Oregon, Australia, Canada and the United Kingdom, the presentation of results will focus on the plausible size of CETs, ethical considerations including debate about the "*rule of rescue*" and the normative assumptions underlying the logic of cost effectiveness, reflective equilibrium issues arising from its use, the relevance of treating patients *as persons* equally, and the implications of CETs as (incremental cost effectiveness) ratios.

Actual CETs have surfaced based on face validity and are not supported by evidence, with estimates varying substantially by perspective (supply or demand side) and measurement method, and likewise between jurisdictions. It is further argued that the quasi-utilitarian construct of social value as an additive aggregate of individual (selfish) health benefits – quantified by a metric combining length and quality of life only, at the expense of other sources of individual and social value – can explain some of the most critical issues arising from the use of CEA and CETs for priority setting in health care.

The most fundamental issues are grounded in the nature of collectively financed health schemes as social institutions, whereas the focus of the aggregation logic is on allocative efficiency at the expensive of distributive objectives. This collides with social norms and preferences implying a priority for caring for those in highest need. Further, the nature of CETs as ratios can explain the difficulty of reconciling their use with fairness-related objectives, to not systematically disenfranchise many patients with rare diseases from access to effective medical care, and the silence of CETs about the budgetary impact and hence affordability of health care programs.

Further limitations result from conventions of a presumably technical nature, such as the focus on evaluating condition-

treatment pairs in applied CEAs, at the expense of considering the high prevalence of co-existing conditions (and the related concentration of cost) among a small number of patients, resulting in the calculation of hypothetical but unrealistic QALY gains and incremental cost per QALY ratios.

International HTA agencies have begun to react to these loop-holes of the conventional cost effectiveness paradigm by intro-ducing modifiers (e.g., for severity and rarity) and by adding budget impact tests, irrespective of the inconsistencies created this way.

Summing up, it is tentatively concluded here that the use of CETs rests on highly problematic assumptions and results in consequences for the access to effective health care that have already led to adjustments by international HTA agencies.

Against this background, health care policy makers may wish to consider alternative methods for priority-setting, which are more flexible to reflect local institutional context, values and objectives of collectively funded health care.

IV

Introduction

In the context of increasing concerns about the sustainability of health care expenditures growing faster than gross domestic product (GDP) in many jurisdictions, the question of setting limits to collectively funded health care has been widely discussed by policy-makers, politicians, and the public alike (Calabresi and Bobbitt, 1978; Callahan, 1987; Aaron, 1995; Fuchs, 1998; Daniels and Sabin, 2002; Altman et al., 2003; Kaplan, 2009; Baumol, 2012; Andersen, 2016; Collins et al., 2023). As part of that discussion, some decision-makers have looked to tools, including variants of Health Technology Assessment (HTA) – defined as "a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle" with the aim of informing decision-making in regards to three objectives, the equity, efficiency, and quality of health systems (O'Rourke et al., 2020).

In adopting HTA, some countries followed the advice from health economists advocating to go beyond comparative clinical effectiveness research and use cost effectiveness analysis (CEA) as a tool to inform decisions on coverage and reimbursement levels of health care programs. Like other types of comparative economic evaluation, CEAs are conducted "to assess the social desirability of a program relative to some other alternatives" (Brent, 2003, p. 4). Since the inauguration of the underlying logic in the 1970s (Torrance et al., 1972; Weinstein and Zeckhauser, 1973; Weinstein and Stason, 1977; Pliskin et al., 1980; Weinstein, 1990; Johannesson and Weinstein, 1993), the number of published CEAs has increased steadily, reflecting wide-spread popularity of the method among health economists (Fig. 1; *Tufts Registry, 2025*).

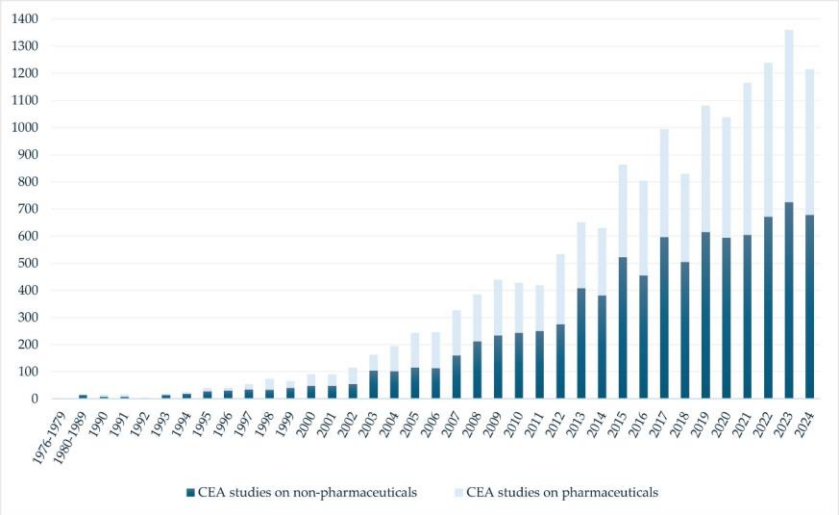


Figure 1: Number of published CEA Studies from 1976–2024

(Source: Center for the Evaluation of Value and Risk in Health. The Cost-Effectiveness Analysis Registry. Boston: Institute for Clinical Research and Health Policy Studies, Tufts Medical Center. Available at *www.cearegistry.org*; last accessed December 01, 2025). The Registry focuses on a subset of CEAs, called CUAs that quantify health benefits in terms of QALYs and/or DALYs. Studies on all health outcomes are included.

CEA, cost effectiveness analysis; CUA, cost utility analysis; DALYs, disability-adjusted life years; QALYs, quality-adjusted life years.

Where adopted officially, CEA has become a significant second pillar of HTAs, intended to answer the question of whether a medical intervention is "efficient" (i.e., "is it worth it" meaning "is it cost effective") – intended to go beyond the questions of the intervention's effectiveness (i.e., "does it work" in actual clinical practice) and its efficacy (i.e., "can it work"; cf. Schwartz

and Lellouch, 1967) – even though in reality many analyses would appear to be better characterized as "cost efficacy evaluations" (cf. Hsu, 2023; Longo, 2023; Nilsen et al., 2025). To be useful in prioritizing across different technologies in different therapeutic areas, the adoption of CEA demands a high level of standardization, including implicit or explicit thresholds for the maximum allowable (incremental) cost per (incremental) unit of health gain - which, if exceeded, are interpreted to signal inefficient use of resources.

The specific appeal of cost effectiveness analysis (CEA) "is that it allows a *convenient* means of *quantifying* both economic and health benefits in *a single ratio*" - i.e., the incremental cost effectiveness ratio ("ICER"), "which permits comparisons *across diverse interventions and diseases*" when health benefits and costs are measured in a common unit (Neumann, 2005, p. 8; *emphasis added*).

Yet the use of cost effectiveness thresholds (CETs) to inform decisions on efficient health care resource allocation has been subject to controversial debate. Proponents of the concept of CETs claim that their use helps to ensure that the adoption of medicines meets criteria of distributive neutrality and hence "fairness" and that it minimizes opportunity costs (Weinstein and Zeckhauser, 1973; Weinstein, 1988; Torrance and Feeny, 1989; Culyer, 1992, 2016; Neumann and Weinstein, 2010; Round, 2012; Drummond et al., 2015; Rid et al., 2015; Rumbold et al., 2017; Charlton, 2020; Rand and Kesselheim, 2021; Kaplan et al., 2024), and that CETs enable balancing patients' access to innovation with financial sustainability of publicly funded health care systems (e.g., Bouvy, 2024). Discussing the use of a CET *range* by the official HTA agency for England and Wales, health economists from the universities of York and Leeds insisted in an influential publication cited more than 1,000 times

in the ensuing literature, "that it is *feasible and probably desirable* [*emphasis added*] to operate an explicit single threshold rather than the current range; the threshold should be seen as a threshold at which 'other' criteria beyond the ICER itself are taken into account," with very few qualifications, such as suggesting that "interventions with a large budgetary impact may need to be subject to a lower threshold…" (McCabe et al., 2008, p. 733).

Others have raised concerns on grounds of normative, empirical, and technical considerations (e.g., Rawles, 1989; Birch and Gafni, 1992, 1993, 2006a; Nord, 1999; Ubel, 2000; Coast, 2004, 2009; Coast et al., 2008a,b; Mooney, 2009; Gyrd-Hansen, 2005; Dolan et al., 2005; Richardson and McKie, 2005, 2007; Schlander, 2005a, 2010; Round, 2012; Schlander et al., 2014, 2016; Smith and Richardson, 2005; Klonschinski, 2016; Mitchell et al., 2017; Goranitis et al., 2017; Richardson and Schlander, 2018; Caro et al., 2019; Cleemput et al., 2011; Rand and Kesselheim, 2021; Wouterse et al., 2023).

International health care policy makers have reacted in different ways. These range from adoption of the standard approach and its promise to provide a single number – the incremental cost per quality-adjusted life year (QALY) gained (in which a QALY is a single metric that combines, by means of multiplication, length of life with health-related quality of life, HRQoL) – to guide decisions on coverage of health technologies on the one hand, to outright rejection of economic analyses (Giacomini et al., 2004; Luebbe, 2015, 2017; Klonschinski, 2016) and sole reliance on clinical effectiveness data on the other hand, without formal consideration of resource use and associated opportunity costs in the HTA process.



Despite the existence of multiple approaches, the presentation of cost effectiveness analyses (CEAs) permeates standard text-books of applied health economics, in particular at the intro-ductory level, and it is what is being taught as *the* standard in medical courses, public health classes, and many university seminars. Specialized academic departments as well as large numbers of contract research organizations and consulting businesses – sometimes overlapping with each other – have emerged that apply the methodology, all-too-often without much reflection of its underlying premises (for example, Sloan, 1996; Donaldson et al., 2002; McCulloch, 2003; Annemans, 2008; Jackson, 2012; Kobelt, 2013; Muennig and Bounthavong, 2016, pp. 1-4).

Problem Statement

While multiple HTA agencies have adopted CEAs, few (if any) have been following the underlying logic without modifications – in particular, their reliance on cost effectiveness thresholds varies greatly. Even NICE, which has been considered broadly as an exemplar of the use of cost effectiveness for priority-setting, has introduced a large number of *ad hoc* modifications.

These observations give rise to important questions regarding the logic of cost effectiveness, including the use of CETs as a tool to inform access decisions. The logic fundamentally rests on the validity of the premise that rankings of interventions on grounds of their increasing incremental cost per QALY gained reflect their decreasing social desirability, and thus lower

priority-ranking, in the context of a collectively financed health scheme.

This is not merely a theoretical or technical issue for debate within academic circles or among health economists. As HTA agencies diverge in their methodologies and the weight given to different evaluation criteria, outcomes of HTAs differ greatly between agencies (Nicod and Kanavos, 2012; Adkins et al., 2017; Allen et al., 2017; Schaefer and Schlander, 2019; Schaefer et al., 2021, 2023; Jenei et al., 2023; Trouiller and Laramée, 2023; Papadopoulos et al., 2025). Importantly, the underlying issues would extend beyond the potentially far-reaching consequences for both patients and payers of selecting an ill-defined CET, if the search for "the right CET" turned out to be a fraught exercise itself.

Research Objective

The present research looks to better understand the use of cost effectiveness thresholds (CETs) in the context of health care policy recommendations and decision-making, with the objective of presenting a critical yet balanced perspective on the roles and limitations of CETs. It will contribute to worldwide dialogues on the appropriate use of CETs in the context of health technology assessment (HTA), and it will throw a spot-light on some of the most salient unresolved and/or contro-versial issues surrounding the use of CETs.

IV

Methods

Approach

With the present publication, we present a timely narrative summary of key findings emerging from an ongoing, much broader project with the objective to provide a comprehensive overview of the international experience with cost effectiveness thresholds (CETs) as a tool to inform health care priority setting, its underlying rationale and its loopholes, and the implications and consequences of their implementation.

For the project, we adopted a critical or integrative review approach that is closely related to the semi-structured review method (cf. Wong et al., 2013), but allows to pursue the broader objective of assessing, critiquing, and synthesizing the available literature on the use of thresholds in the context of cost effectiveness analyses (CEAs) in a way that enables new theoretical frameworks and perspectives to emerge.

Our purpose has been to assess and review the existing knowledge, with a view towards subsequent next steps beyond the present paper – to potentially reconceptualize, and to expand on the theoretical foundation of the specific topic. Ultimately, the project is expected to contribute to the advancement of knowledge and theoretical frameworks, rather than providing a simple description and overview of the research field (cf. Torraco, 2005; Whittemore and Knafl, 2005; Hopia et al., 2016; Snyder, 2019). It is intended to then analyze the potential of alternative approaches proposed as decision support methods in the HTA context, including policies regulating access to medical technologies and their reimbursement and pricing.

Search strategy

To search for relevant literature, we used a combination of four strategies designed to complement each other:

i. Textbook-based search

   Identification of references from *health economics* standard textbook chapters (Gold et al., 1996; Culyer and Newhouse, 2000; Glied and Smith, 2011; Drummond et al., 2015; Neumann et al., 2017), which were screened by title for literature cited, covering the period from 1996 to 2017 (i.e., years of publication of textbooks; cf. Appendix, Fig. A1);

ii. Database search

   Systematic literature search in the electronic databases Medline / PubMed, Scopus, and Web of Science (WoS) for recent references (including review articles) by title and abstract screening in the peer-reviewed literature covering the period from January 2015 to August 2024 (cf. Appendix, Fig. A2; for individual search strings, cf. Appendix, Tab. A1);

iii. Gray literature search

   Potentially relevant gray literature was identified by the authors, including policy papers issued by governmental institutions, regulatory bodies and official health technology assessment (HTA) agencies;

iv. Seminal or defining papers

   Inclusion of seminal or defining papers recommended by external experts.

Simultaneously, we applied "snowballing" or "citation mining" (sometimes also referred to as "comprehensive pearl growing"; cf. Greenhalgh and Peacock, 2005) as a supplementary search

technique to identify further relevant literature (Schlosser et al., 2006). This involved a smaller number of primary articles – typically textbook chapters and recent reviews in the peer-reviewed literature – that deal with CEA for health care resource allocation decisions. From these primary articles, both backwards and forward searches have been done, i.e. backwards, articles cited in the bibliography were checked for eligibility for inclusion in the analysis, and forwards, articles that have cited the primary articles were checked, too.

Further *ad hoc* searches in the electronic databases were added to identify publications related to specific topics that emerged during the prior systematic search, such as "the rule of rescue", and finally, we added most recent literature that appeared after the search periods in an opportunistic way, such as updates on the changes of the CET and budget impact test in the NHS England effective April 1, 2026.

Analysis

For documentation of the records identified by the textbook (i.) and database (ii.) searches – extended by relevant gray literature (iii.) and seminal / defining papers (iv.), the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) flow diagram was used. After identification of the records and the removal of duplications, titles and abstracts were screened for their relevance. If the article was not consistent with our research objective (e.g., when the title or abstract did not indicate that the paper addressed the use of thresholds in the context of CEA), it was excluded (see Appendix, Figs. A1 and A2).

Once an article was included based upon its title / abstract, the full paper has been retrieved and assessed for eligibility criteria (cf. Appendix, Tab. A2) by two independent researchers (RS and MS).

In this process, references were also classified to fall into one of the following categories, which had been informed by an *a priori* framework following the envisaged structure of the review. We (sub-)categorized the papers as follows:

a. Theoretical
    (a) normative economic
    (b) normative philosophical / ethical
    (c) assumptions of a presumably "technical" nature

b. Empirical
    (a) economic – derivation of thresholds
    (b) economic – application of thresholds
    (c) (stated) objectives of health care systems and HTA
    (d) issues arising from implementation of thresholds

c. Regulatory / Policy-related
    (a) peer-reviewed
    (b) gray literature (e.g., policy recommendations, guidelines from HTA agencies)

Of the 3,586 records initially identified through textbook (n = 2,353) and systematic database searching (n = 1,233), 479 studies of potential interest were left after removal of duplicates and title / abstract screening (textbook search, n = 340; database search, n = 139, plus 12 studies from reference search). In addition, we included 27 papers we deemed seminal, and 11 gray literature publications. After the assessment of eligibility criteria, a total of 154 theoretical (see *Supplement: A. List of Theoretical Literature*), 198 empirical (see *Supplement: B. List of*

Empirical Literature) and 47 political / regulatory (see *Supplement: C. List of Policy-Related Paper / Regulatory Documents*) papers were included. While theoretical literature encompassed *normative* economic, ethical, and philosophical studies, regulatory and policy-related papers incorporated both peer-reviewed articles and gray literature publications. The empirical literature included primary and /or secondary research studies – either based on quantitative or qualitative data, as well as meta-analyses and / or reviews. – *Supplementary* literature documentation, beyond *References* cited and information given in the *Appendices*, will be provided on request.

Finally, we used an inclusive sampling approach by selecting articles explicitly relevant to understand the use of thresholds in the context of CEA. This means the extracted information was synthesized to provide a comprehensive and structured overview of CEA thresholds through narrative analysis, based on a qualitative research method involving the systematic examination and interpretation of textual data to identify pros and cons of their theoretical and practical use.

Pros and cons identified from the selected articles were then assigned to more specific themes, such as the underlying approach, concept, dimensions (e.g., related to costs) and preferences (e.g., related to severity). Theoretical, empirical and practical elements were derived from more than 74 articles to *better* understand and *critically* reflect on the use of CETs, as well as to provide a more balanced perspective on the role and limitations of cost effectiveness benchmarks in the context of HTA and health care decision making.

As stated above, we added most recent literature that appeared after our search periods in an opportunistic way.

IV

Key Observations & Discussion

In this article, we provide a timely first abridged report of our emerging findings, offering insight into some major implications for policy makers interested in the economic evaluation of health care programs. We outline how the use of CETs evolved over time, then turn to issues and controversies experienced in jurisdictions that have historically relied on CETs to inform coverage decisions, and we analyze underlying causes and outcomes. To better understand the logic of CEA and CETs in practice, we begin by looking back to its early years, where the approach was looked at in an effort to decide which health technologies should be covered and reimbursed by health care schemes (cf. Tab. 1, below).

How CETs have been used to prioritize coverage and reimbursement decisions

In order to prioritize the funding of health interventions based on a CET approach, mutually exclusive interventions were to be ranked on the basis of their incremental (not average) cost per QALY gained, putatively reflecting an increasing social desirability with decreasing incremental cost effectiveness ratios (ICERs). Such rankings are usually referred to as cost effectiveness "league tables" (Williams, 1985a,b; Drummond et al., 1987, 1993, 2015; Mason et al., 1993; Birch and Gafni, 1993; Mauskopf et al., 2003; Wilson et al., 2019; Carvalho et al., 2022).

The aim of maximizing health benefits at the population level, defined as the sum total of QALYs produced, then dictates that funding of health care programs should begin with coverage at

the top of the list (or cost effectiveness league table) and continue to do so down until the point is reached when resources have been extinguished, i.e., "at which society is no longer willing to pay the price for the benefits achieved" – as it is claimed (Weinstein and Stason, 1977, p. 717). Using a "demand-side" decision rule, the validity of the cut-off level is directly linked to the maximization assumption and the societal willingness to pay (WTP) for a QALY – identical with the notion of a fixed cost effectiveness threshold (CET) or "lambda" (Weinstein and Zeckhauser, 1973; Johannesson and O'Connor, 1997).

As an alternative view, other authors proposed that the CET should be interpreted as the shadow price of health under a fixed budget, i.e., a "supply-side" opportunity-cost threshold, estimated from a given health-system's marginal productivity (Drummond et al., 1987,2015; Claxton et al., 2015; Ochalek and Lomas, 2020; Ochalek et al., 2021; Sampson et al., 2022; Vallejo-Torres et al., 2022).

The Oregon Health Plan (OHP) experience

The Oregon Health Plan (OHP), which dates back to 1989, represented the first serious attempt to formally implement explicit health care prioritization policies on grounds of the logic of cost effectiveness (Jacobs et al., 1999; Oberlander et al., 2001). A Health Services Commission was set up to compile information on clinical effectiveness, treatment cost, and community values. In practice, it reduced over 10,000 services to a list of 709 condition / treatment (C-T) pairs (the number changed subsequently), which were ranked based on their *net health benefit*, i.e., their putative cost effectiveness. Contrary to

initial expectations, the OHP failed to prove itself as an effective cost containment instrument, with OHP managers estimating that the plan saved Medicaid only two percent on its total expenditures over the first five years (Office of Medical Assistance Programs, OMAP 1997, ES3). Originally "the aim of the 'prioritization' process was to allocate Medicaid funds in a more sensible, systematic, and utilitarian manner - benefiting the greatest number of recipients possible within limited resources" (Jacobs et al., 1999). Covered services were those above the cut-off line, which was determined by the level of funds available for the program. Services below the line were not to be covered. The list of services covered would be (and in fact was repeatedly) reduced in case of a budget shortfall, and changes could be made in light of new information (Rosenbach et al., 1997).

Even if not quantified explicitly, the initial cut-off line was the equivalent of an implicit CET - as Weinstein and Stason (1977, p. 717) had postulated, it became the "cut-off level of permissible cost per unit of effectiveness." In reality, the first draft list of about 1,600 medical procedures was never implemented. It implied counterintuitive priorities, such as ranking crooked teeth higher than early treatment for Hodgkin's disease, or giving higher priority to dealing with thumb sucking than hospitalization of a child for starvation or treatment for AIDS (Fox and Leichter, 1991, p.22; Tengs et al., 1996; p. 101). As a result, the list was scrapped and replaced by a new version, comprising nearly 800 C-T pairs, which were ranked based on "public values and clinical judgment" - i.e., relying heavily on negotiations and the "own values and judgments" of the commission members (Castanares, 1991, quoted after Fox and Leichter, 1991).

Table 1: International Milestones of Applied Health Economics

Oregon Health Plan (OHP, since **1989**) ¬ debate about the "rule of rescue" ¬ legal ban of cost/QALY use in the United States (ADA, ACA / PCORI, IRA)
New Zealand (PHARMAC Core Service Committee, since **1992**)
Australia (PBAC / PBS, since **1993**)
Canada (CDA-AMC / INESSS, since 2024) ¬ established as CCOHTA in 1989 (CADTH, since 2006) ¬ first cost effectiveness guidelines for pharmaceuticals issued in **1994**
England and Wales (NICE, since **1999**)
Germany (IQWiG, since 2004) ¬ proposing "efficiency frontier analysis" as an alternative approach (**2009/2010**)

ACA, Affordable Care Act; ADA, Americans with Disabilities Act; CADTH, Canadian Agency for Drugs and Technologies in Health; CCOHTA, Canadian Coordinating Office for Health Technology Assessment; CDA-AMC, Canada's Drug Agency - L'Agence des médicaments du Canada; INESSS, Institut national d'excellence en santé et services sociaux; IQWiG, Institute for Quality and Efficiency in Health Care; IRA, Inflation Reduction Act; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; PCORI, Patient-Centered Outcomes Research Institute; PHARMAC, Pharmaceutical Management Agency.

As research on the OHP approach continued, more fundamental conceptual issues were identified. Two linked surveys revealed that rankings predicted by the logic of cost effectiveness deviated significantly from the rationing choices of the same individuals. Their rationing choices suggested that they placed tenfold to one-hundred-thousand-fold higher relative values on treating severely ill people and on the importance of saving

lives than their utility choices would have implied. The authors observed that "the subjects soundly rejected the rationing choices derived from their utility responses" (Ubel et al. 1996a, p. 108).

Thresholds in countries using CETs

Despite the limitations of these first efforts, in the ensuing years after the Oregon experiment CEA became an integral part of formal Health Technology Assessment (HTA) processes in some national jurisdictions, with Australia and Canada cited as the forerunners, which were most notably followed by the United Kingdom (UK). These countries incorporate CEA as a main decision criterion in HTAs, relying on different explicit or implicit thresholds. Other countries where HTA is in its infancy often look to these prominent examples as potential role models (cf. Kumar et al., 2025). Still, the level of CETs varies greatly from country to country, and indeed even within a country.

Australia

In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) does not have a formal policy with regards to the maximum acceptable cost per QALY and hence no explicit CET. However, widely cited retrospective analyses suggested not only a positive relationship between higher incremental costs per additional life year gained and the likelihood of rejection of an application for funding, but more specifically, acceptable ICERs in a range between AUS-$ 42,000 and AUS-$ 76,000 per life year gained (1998/99 values; George et al., 2001) or a mean CET of AUS-$ 46,400 per QALY gained (2004 values; Harris et

al., 2008). Beyond cost effectiveness, clinical significance, cost to government (net budgetary impact; cf. subsequently also Mauskopf et al., 2013, and Turkstra et al., 2017), and severity of disease were found to exert a significant influence on recommendations. In particular, drugs for life-threatening conditions had higher probabilities of being evaluated positively (Harris et al., 2008).

Early on, concerns were raised about reduced access to cancer medicines due to their higher ICERs compared to non-cancer drugs. A rejection rate of 56% for anticancer drugs was reported on grounds of an analysis of 213 submissions between 2005 and 2014 to PBAC for listing with the PBS, with "inadequate cost effectiveness" being the most frequently offered reason by the PBAC (Karikios et al., 2017). Further analyses indicated that, over time, the PBAC became "increasingly reluctant to recommend pharmaceuticals beyond a cost effectiveness ratio of AUS-$ 45,000 per QALY", confirming the "inverse relationship between the CER and the probability of reimbursement" (Ngo, 2014). A subsequent study of PBAC submissions from 2010 through 2018 (Lybrand and Wonder, 2020) reported no substantial change over time, with no medicines recommended by the PBAC for listing with the PBS if their ICER exceeded AUS-$ 75,000. This analysis excluded vaccines evaluated for the National Immunisation Programme and those reviewed and subsequently listed on the Life Savings Drugs Programme (LSDP).

Canada

In Canada, despite some exceptions, in practice a CET of CAN-$ 50,000 per QALY gained is being applied (Griffiths and Vadla-mundi, 2016; Binder et al., 2022; Rawson, 2022; Balijepalli et al.,

2024). While in earlier CEAs the Canadian Agency for Drugs and Technologies in Health (CADTH; succeeded by Canada's Drug Agency / L'Agence des médicaments du Canada, known as the CDA-AMC, since May 2024) often made reference to the impact of using a CET of either CAN-$ 50,000 or CAN-$ 100,000, analysts reported that, beginning in late 2020, CADTH apparently moved to use only the lower CAN-$ 50,000 benchmark (Binder et al., 2022).

In the context of intense controversial debates concerning the impact of Canada's CET and its complex evaluation and decision processes on patient access to drugs for rare diseases and for oncology indications (Adkins et al., 2017; Salek et al., 2019; Rawson, 2022; Ward et al., 2022; Rawson and Stewart, 2024), CDA-AMC announced process improvements, introducing a new "Time-Limited Recommendation" (TLR) category accompanied by a temporary access process, essentially a new path to conditional reimbursement similar to coverage with evidence development schemes in other jurisdictions (Glennie et al., 2022; Cowling et al., 2023).

United Kingdom (England and Wales)

In England, the National Institute for Health and Care Excellence (NICE) – established 1999 as National Institute for Clinical Excellence, mandated with technology appraisals binding for the NHS in England and Wales - is frequently portrayed as *the* international role model for the implementation of CEA (cf. Kumar et al., 2025). NICE initially denied having any benchmark for cost effectiveness at all, "and it only softened its position when it emerged from analyses of its decisions that it had some kind of benchmark zone" (Williams, 2004; pp. 7f.). Independent academic research (Raftery, 2001, 2006; Towse and

Pritchard, 2002; Towse et al., 2002) studies (Devlin and Parkin, 2004; Dakin et al., 2006) revealed the "range of acceptable cost effectiveness" applied by NICE in reality. Subsequent analyses confirmed the decisive role of cost per QALY gained for NICE's technology appraisals (Dakin et al., 2015; Schaefer and Schlander, 2019; Schaefer et al., 2021, 2023), with cost effectiveness alone correctly predicting 82% of NICE decisions according to binary choice analyses (Dakin et al., 2015).

According to a speculation popular among health economists, the standard benchmark used by NICE in England of £20,000 to £30,000 per QALY gained was derived from an early estimate for the cost effectiveness of renal dialysis in the U.S. in the 1970s of approximately US-$ 50,000 per QALY gain (Neumann et al., 2014). As Michael Rawlins, foundation chairman of NICE, explained in an interview in 2009, "The £30,000 emerged. I've always said that it's not locked in some empirical basis. It emerged. And it emerged during the first year or two of the appraisal committee meeting. It didn't become enshrined as a formal number until about 2002, 2003 [...]. There's no empirical research on which to base it, but increasingly it looked as if this judgement, as you might call it, on behalf of the appraisal committee and particularly the health economic community, is probably around the right ballpark" (Timmins, 2009; Appleby, 2017, p. 161).

Jacoline Bouvy, the NICE Programme Director for Medicines Evaluation, stated in 2024: "If the incremental cost-effectiveness of a new medicine is above £20,000 per QALY gained, then our committee must explicitly consider whether they can still recommend the medicine. […] NICE's focus when evaluating new medicines remains clear: making decisions that balance innovation with financial sustainability […]." Mentioning "innovation" and "sustainability" implies consideration of

"dynamic efficiency" and "affordability" as (secondary) objectives, claims that have proven controversial and will be revisited below. Of note, NICE had insisted earlier that it "does not take the budget impact of a new technology into account" and that "[a]ffordability is not the responsibility of NICE" (Pearson and Rawlins, 2005, p. 2619; cf. Tab. 2).

Table 2: Major Iterations of England´s Approach since 1999

The NICE Cost Effectiveness Threshold
¬ NICE Methods Guide and Reference Case (**2004**)
¬ official benchmark (CET) and Social Value Judgments (**2004/2005**; **2008**)
¬ CET adjustment (**2025**, change was introduced from **April 2026** onwards)
NICE End-of-Life Guidance (**2009**)
¬ permitting violation of NICE's CET if treatment is limited to a small terminally ill patient population
¬ replaced by **Severity Modifier** (**2022**)
Cancer Drugs Fund (**CDF**, **2011**)
¬ reconfigured in 2016, essentially converted into a managed access scheme
NICE Single Technology Appraisal Process (**STA**, **2005**)
Highly Specialised Technology Process (**HST**, **2013**)
¬ new restrictive routing criteria introduced in **2025**
Ethical principles officially adopted by NICE
¬ fundamental equity position (QALY Egalitarianism, **2004**)
¬ submission to Daniels & Sabin (A4R), **2005**
¬ submission to Beauchamp & Childress (Medical Ethics, 1979), **2008**
Budget Impact Threshold (**BIT**, **2017**)
Adjustment of BIT and CET (2026)

A4R, accountability for reasonableness; CET, cost effectiveness threshold; QALY, quality-adjusted life year; NICE, National Institute for Health and Care Excellence.

Using data from all NICE decisions until end of 2011, a team led by Helen Dakin from the University of Oxford concluded in 2014 "that technologies costing £40,000 per quality-adjusted life-year (QALY) have a 50% chance of NICE rejection (75% at £52,000/QALY; 25% at £27,000/QALY). Past NICE decisions appear to have been based on a higher threshold than £20,000–£30,000/QALY. However, this may reflect consideration of other factors that cannot be easily quantified." More recent analyses confirmed these observations while suggesting increasingly "greater caution [by NICE] in the application of higher decision-making thresholds (Taylor et al., 2025).

Until most recently, the threshold in the UK had not changed since it had emerged over twenty years ago despite inflation reducing its value by 50% in real terms (Ubel et al., 2003; Neumann et al., 2014; ABPI, 2025). On December 1, 2025, the UK government announced a rise of NICE's standard threshold from £20,000-£30,000 to £25,000 to £35,000 per QALY gained, which NICE implemented effective April 1, 2026 (NICE, 2025). This decision was made as part of a trade deal between the UK and the United States (Robertson, 2025a) – hereby highlighting the political, technocratic nature of NICE's CET – very much so to the annoyance of many health economists who support the logic of cost effectiveness (cf. e.g., Vallejo-Torres et al, 2026).

Rejection of CE Approaches to HTA and Decision-Making

Despite the use of CETs in some countries, many others have explicitly chosen not to use cost per QALY gained CETs and taken a different approach to value assessment and decision-making altogether. In Germany, the official Methods paper

issued by the Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, IQWiG) in 2009, noted that "in many countries cost-utility analyses based on QALYs are not accepted by decision makers and clinicians due to concerns regarding solidarity, equity and fairness" (IQWiG, 2009, p. 3). IQWiG insisted that health economic evaluation in Germany should not be performed *across* indications, but only *within* individual therapeutic areas (IQWIG, 2009, p. 19; *emphasis added*), and by implication rejected the use of a CET. As a consequence, the official German HTA process has relied on comparative effectiveness analyses of (additional) clinical benefit only, heavily drawing on data from randomized clinical trials (Scriba and Middeke, 2007; Ruof et al., 2014a,b; Blome et al., 2017; Wagle et al., 2021; Schlichting et al., 2022; Bartol et al., 2023). In the latest iterations of its methods guide and related consultation documents, IQWiG also rejects the idea of uniform CETs in the German context (IQWiG 2023, p. 11; IQWiG, 2025, p. 97).

In France, the evaluation process resembles in many respect the early benefit assessment process in Germany, as both rely on well-defined scales defining the added value of a new product based on its clinical effectiveness (Fernandez et al., 2025). In 2013, CEA was implemented as a complementary part of the formal evaluation process in France, but no specific CET is used within the French HTA context (de Pouvourville, 2013; Ghabri, 2024).

Because of the perceived lack of a sufficient theoretical and scientific basis, including controversy around its estimation and what the threshold should represent, no CETs have been formally adopted by the official institutions in Italy and Spain (cf. e.g., Akehurst et al., 2017; Frontrier et al., 2022). HTA decisions in Italy and Spain are guided by an evauation of

clinical effectiveness and a number of criteria (such as disease burden, unmet need, and added therapeutic value), including cost effectiveness analyses but without a uniform threshold across indications (Russo et al., 2023).

Finally, it seems noteworthy that across the broader European Union Joint Clinical Effectiveness process, there is no value assessment or economic evaluation, given that such judgments, along with the regulation of their respective health and social systems, remain in the remit of the EU member states. The nonapplication of cost value – or more specifically cost effectiveness – assessments on the European level underscores that there is no "one size fits all" solution to the valuation of health care technologies across European jurisdictions, reflecting the relevance of their heterogeneity in economic, political, legal and institutional context, national and societal preferences, and social norms (Löblová, 2016; Angelis et al., 2018; Pinheiro et al., 2025; Fernandez et al., 2025).

Methodological Challenges: The plausible size of a CET

Historical thresholds have not been established scientifically. Rather, as exemplified by NICE (see above), the CETs used by some HTA agencies "emerged." Some approaches to rationalize CETs follow an economic "demand-side" logic, seeking to establish a willingness-to-pay (WTP) based on the value of a life year or value of health gained (Hirth et al., 2000; Mrozek and Taylor, 2002; Viscusi and Aldi, 2003; Nimdet et al., 2015; Ryen and Svensson, 2015; Schlander et al., 2017, 2023; Loupas et al., 2026). Hirth et al. from the University of Michigan analyzed the

empirical economic value-of-life literature, deriving a range of estimates between 93,000 and 428,000 US-$ (1997) per QALY (Hirth et al., 2000). Another recent systematic review and analysis of the economic literature published between 1995 and 2020 (Schlander et al., 2023) found 169 unique estimates for the value of a statistical life, translating into a median value of a statistical life year (VSLY) of 168,367€ (2019; mean, 256,701€), and with substantial differences not only by region (e.g., North America vs. Europe), but also by valuation method (panel or cross-sectional study design, contingent valuation / stated preferences, or revealed preferences).

Other approaches are "supply-side" driven, relying on health-system opportunity costs within a given fixed budget envelope. Such research is based on the central assumption that health care budget holders simply seek (or at least ought, cf. Culyer, 1997) to maximize the number of QALYs produced, which is known not to be the case in reality. This approach has been inspired by work by Karl Claxton and colleagues (2013, 2015) from the University of York, who used econometric modeling techniques to estimate the statistical relationship between changes in mortality in certain Programme Budget Categories (PBCs) and differences in expenditures across different Primary Care Trusts (PCTs, now replaced by Clinical Commissioning Groups, CCGs) in England, and computed a much-cited point estimate (Claxton et al., 2013, p. viii) of the marginal cost per QALY gained in the NHS at £12,936 (for 2008 expenditures and 2008-2010 mortality; Claxton et al., 2013, p. 60).

Subsequent analyses for the NHS England – following the same logic of "health care opportunity costs" – estimated that the marginal productivity might be even lower, between around £5,000 and £10,000 per QALY gained (Lomas et al., 2019; Martin et al., 2021). Many further studies were published by scholars

close to NICE International or the York group around Karl Claxton; they used either econometric modeling (Ednay et al., 2018, 2022; Ochalek et al., 2018a, 2018b, 2020; Ochalek and Lomas, 2020; Lomas et al., 2019, 2022a,b; Pichon-Rivière et al., 2023; Vallejo-Torres et al., 2018, 2023) or extrapolation techniques (Woods et al., 2016; Al-Jedai et al., 2023) to derive CETs for many international jurisdictions, or to compare so-defined "health care opportunity costs" across different countries (Vallejo-Torres et al., 2022). Importantly, as noted, all rest on the assumption that health care budget holders (PCTs or CCGs in the case of the NHS England; Claxton et al., 2013, 2015) seek (only) to *maximize* the number of QALYs produced – despite the fact that the validity of the maximization hypothesis has been questioned early on. For example, early reviews of the original Claxton study pointed to the contradictory "finding in Appleby (2009) that [clinical and other] non-economic factors are often the basis for spending undermines this assumption" (Barnsley et al., 2013, p. 54).

Still, NICE has been subject to critique based on the normative assumptions inherent in the CET estimate by Claxton and colleagues (2013, 2015). For example, Naci et al. (2025) recently calculated with reference to a benchmark of £15 000 to generate an additional QALY (citing Claxton et al., 2015, and Lomas et al., 2019) that NICE guidance had a population-health impact which was negative, resulting in a cumulative net loss of approximately 1.25 million QALYs during 2000 to 2020. Their article was interpreted by a commentator that it "contributes to existing evidence that decisions by NICE might not be ethically justified" (Charlton, 2025), implying that the CETs used by NICE might be too high. Yet, beyond technical problems and over-interpretation of the estimation itself (cf. Sampson, 2025), such calculations are relevant only if one is prepared to "accept

that QALYs capture all of the value generated by health interventions, every QALY is worth the same, and QALY maximization is the *only* goal of the NHS. [… Otherwise,] there is no ethical problem in some QALYs being more expensive than others" (Holm and Schlander, 2025).

In economics "opportunity costs" represent the *value* of the next best alternative that is not chosen. Thus, the concept of "[health] opportunity costs" applied in the studies mentioned before rests on a valid *valuation* principle. To reiterate, the QALY aims to capture three components (i.e., length and quality of life gained weighted by risk) and combines them in a specific way. As such, it excludes by definition any additional sources of (individual and, in particular,) social value (e.g., related to severity, equity, end-of-life care; caring externalities, and in general, respect for patients as individuals with "rights" and "dignity"; cf. further below). Therefore, a "QALY-only" defined "health opportunity cost" threshold is incompatible with priority-setting considering the social value of health care (cf. Nord et al., 1995; Dolan et al., 2005; Gyrd-Hansen, 2005; Smith and Richardson, 2005; Brouwer et al., 2008a,b; Donaldson et al., 2011; Whyle and Olivier, 2021; Holm and Schlander, 2025).

The World Health Organization (WHO), with its CHOICE ("Choosing Interventions that are Cost-Effective") project, introduced the idea of adjusting CETs by the ability-to-pay of a society, i.e., using a ratio based on a country's GDP per capita. CHOICE was launched by the World Health Organization (WHO) in 1998 as an initiative to promote sectoral CEAs on a global scale – with the objective to help policy makers to prioritize health care programs based on impact and cost-effectiveness. The WHO reasoned that an acceptable CET (per disability adjusted life year, DALY, gained) of one to three times gross domestic product (GDP) per capita might be used as a

benchmark (WHO, 2001, 2003a,b; 2015; Edejer et al., 2003; Bertram et al., 2016, 2021).

Given that the WHO recommendation has been repeatedly interpreted as a threshold to be used as a decision rule (cf. Marseille et al., 2015), it should be noted that the WHO insisted that "it was always assumed and intended that other considerations relevant to local settings would be used in decision-making" (Bertram et al., 2016, p. 926). The WHO team endorsed instead context-specific processes for decision-making that are "supported by legislation, [have] stakeholder buy-in and [are] consistent, fair and transparent" and recommended that "cost-effectiveness ratios [...] need to be considered alongside affordability, budget impact, fairness, feasibility and any other criteria considered important in the local context" (Bertram et al., 2016, p. 927). The WHO noted explicitly that "over-reliance on cost-effectiveness ratios and a fixed cost-effectiveness threshold [...] may result in the wrong decisions being made" (ibid., p. 926) and the WHO "never recommended this practice" (ibid., p. 927).

From a *theoretical* perspective, there has been debate about the near-equivalence of the logic of cost effectiveness and economic welfare theory (Birch and Gafni, 1992; Bala et al., 2002; Dolan and Edlin, 2002; Buchanan and Wordsworth, 2015). Some proponents of CEA contend that, under a fixed decision threshold (λ), CEA is (nearly) equivalent to cost-benefit analysis, since accepting interventions with ICER $\leq \lambda$ is algebraically identical to maximizing net monetary benefit (Phelps and Mushlin, 1991; Donaldson, 1998; Breyer et al., 2009; Buchanan and Wordsworth, 2015). However, claims of near-equivalence rest on restrictive assumptions and the purported alignment with economic welfare theory remains contested. The need (for a CET approach to hold) to impose one unique WTP for a

QALY, irrespective of context, has been shown to be *theoretically unattainable* (Gyrd-Hansen, 2005) – among the reasons being that "CEA […] suppresses any variation across income / social groups in utility derived from improvements in health" (cf. Bobinac et al., 2010) and that "one sole WTP per QALY value will entail overriding individual preferences such as diminishing marginal utility of health and potential differences in the value of incremental health across population groups" (Gyrd-Hansen, 2005, p. 423).

Perhaps unsurprisingly, there has also been great interest by HTA policy makers and by industry in the actual adoption and size of CETs from an empirical perspective. Recent surveys show consistently that only a small number of jurisdictions use explicit CETs, that both explicit and implicit thresholds demonstrate wide variation, which cannot be explained on grounds of GDP per capita, and that many of those countries using CETs apply formal modifiers for rarity, severity, and specific therapeutic areas (Strohmaier and Zechmeister-Koss, 2024; Charles River Associates, 2026; Murphy et al., 2026).

Ethical Considerations: The "rule of rescue," social preferences, measurement challenges

Cost effectiveness thresholds raise a number of ethical challenges. To begin with, the (quasi act) utilitarian approach of cost effectiveness analysis, which maximizes efficiency, conflicts with the "rule of rescue" - a term coined by Albert Jonsen in his seminal paper "Bentham in a Box" from 1986. Sean Sinclair offers two examples, "the Chilean government's 2010 rescue of the miners stuck in the Copiapó mine, [and] the Australian

government's 1997 rescue of the lone yachtsman Tony Bullimore, lost in the Southern Ocean after his boat had capsized," and asks what the public's reaction would have been "if a minister had announced that she would not authorize the rescue because the cost per life year was estimated to be 20% above the normal threshold for healthcare interventions, and she intended to use the budget to extend more lives via healthcare interventions" (Sinclair, 2021, p. 31, quoting Burrell, 1997, and Farnsworth, 1997).

Shepley Orr and Jonathan Wolff (2015), among others, while recognizing that there is no doubt that "the rule of rescue has a strong intuitive pull," argue that its application under constrained resources can be justified only at the bedside level. At the program level, in contrast, it would be irrational as a resource allocation principle, i.e., "to decide which tools of rescue to provide" (Orr and Wolff, 2015, p. 537r).

The institutional distinction between the bedside level (or the "emergency room") and the "committee room" (Orr and Wolff, p. 533) is closely related to the distinction between identified and statistical lives introduced by Thomas Schelling (1968) and Charles Fried (1969), and a great deal of psychological and philosophical literature has dealt with the relevance of being visible, i.e., the "identified person bias" (in the first place, being meant descriptively, cf. Cohen et al., 2015; Small, 2015). It has been argued by many that the "visibility" of a disaster victim is a morally irrelevant category (Schelling, 1968, pp.127f.; Cookson et al., 2008; Cookson, 2013; Orr and Wolff, 2015; Charlton, 2022a).

Moral justification of the phenomenon seems indeed impossible in an act utilitarian framework (and the conventional logic of cost effectiveness as a reduced variant hereof), whereas rule

utilitarian reasoning might call on the utility of living in a society in which "people are standing together, sharing hope and fear, and supporting each other in the face of […] disaster" (Verweij, 2015, p. 145). This form of collectivist rationality has been referred to as "constitutive solidarity" (Dawson and Verweij, 2012), as an appeal to distributional fairness (Daniels, 2012), or elsewhere as claiming the "symbolic value" that "we demonstrate the value we place on human life" (Fried, 1969, p. 1425). All of these suppose "that the benefits of live-saving rescues go beyond the lives saved" (Daniels, 2015, p. 114), because, "[f]rom the perspective of the community, solidarity is both instrumentally and intrinsically valuable" (Verweij, 2015, p. 146; cf. also McKie and Richardson, 2003, pp. 2411ff.).

In defense of the rule of rescue, non-consequentialists have insisted on "expressing equal concern" for each person (Dworkin, 1977, p. 272), "as each person's loss is to be regarded as equally significant" (Klonschinski, 2016, p.144), arguing for a moral duty to rescue individual persons in immediate peril.

Fundamentally, the logic of cost effectiveness – and hence the use of CETs – provides a tool to support priority-setting that meets only the criterion of efficiency (defined in narrow terms of QALY maximization), whereas collectively financed health schemes also have goals unrelated to health maximization, in the health economics literature sometimes referred to as "other" objectives, i.e., "equity, need and solidarity [and cost-effectiveness]" in the example of Sweden (Persson, 2012), or "fairness, reasonableness, lawfulness, legitimacy [and health]" as the "primary cluster" of values (Charlton and DiStefano, 2024), or to respond to the clinical *needs* of patients as individuals as required by the NHS England Constitution (Department of Health, 2015).

Critical assumptions

A second ethical challenge can be identified in the underlying assumptions of the cost effectiveness approach: It hinges on the assumptions that (1) QALYs capture the full value of health and health care, (2) all QALYs are at least in principle of equal value, i.e., that health gains are considered of equal value, regardless of who gains and who loses them (Weinstein, 1988, 2009, p. S8; Feeny and Torrance, 1989, p. S193; Torrance and Feeny, 1989), (3) additive aggregation of QALY gains map into the social value conferred – and (4) the clinical needs of patients *as individuals* are taken seriously by this approach. The validity of these assumptions will have far-reaching implications for the normative status of the logic of cost effectiveness and, by implication, of CETs.

The first two assumptions are critical given the tradeoffs inherent in a thresholds approach. If (assumption 1) not *all* elements of value are properly included and combined in the QALY computation and aggregation process (and its implied linearity assumptions), it must be expected to skew tradeoffs across patient groups. The second assumption (2) is related to the first and entails a particular equity position, namely the disregard of any specific features of the respective health states or of the patients themselves.

Many studies have been designed to explore the impact of "contextual factors", such as severity of health state, age of affected individuals, and others (e.g., Schlander et al., 2014; Gu et al., 2015; Lancsar et al., 2020; Loupas et al., 2026). Despite substantial heterogeneity in their design, they support the notion that "valuations appear to vary depending on the nature of the health gain and the characteristics of the beneficiary –

whether real or hypothetical" (Loupas et al., 2026). In sum, these studies provide strong evidence against the normative premise that all QALYs are valued equally, which is one of the implicit or explicit starting points of CEA applying CETs (cf. Weinstein, 1988).

It has been asserted that the fact that CEA does not account for the distribution of health gains (or, for that matter, QALYs) on different persons constitutes "distributive neutrality" (cf. Nord, 1999). Given the postulated objective to maximize expected [health-related] utility and thus QALYs (von Neumann and Morgenstern, 1944; Culyer et al., 1971a,b; Weinstein und Stason, 1977; Feeny and Torrance, 1989; Culyer, 1997), it has been further argued that health gains will even out, because "[t]he axioms [of expected utility theory] define rational behavior and their repeated application ensures that] the probability that the achieved utility differs from the maximum achievable utility by an arbitrarily small number approaches unity" (Marschak, 1950, p. 139).

Already Weinstein and Stason had realized that the aggregation of benefits and costs from the individual level to the population level implied that "a single cost-effectiveness measure will not do" in case of concerns for an equitable distribution of costs and benefits. Yet, they suggested that "over large numbers of programs and practices the inequities are likely to even out and, with some exceptions, may reasonably be ignored" (Weinstein and Stason, 1977, p. 718). This position raises several issues.

First, the *compensation problem* as a normative issue inherent in interpersonal aggregation because, as had been argued early by Eric Rakowski (1991, p. 303), life-saving decisions are indivisible and may only occur once in a lifetime of many patients– in such cases, there won't be any later compensation possible for

patients (or patient groups) who were disenfranchised from access to a needed treatment for a life-threatening or otherwise catastrophic condition; cf. also Rakowski, "Taking and saving lives" (1993), and Luebbe (2004, p. 163). Amartya Sen objected forcefully that, "as John Rawls has argued in disputing claims of utilitarianism, distribution-indifference does not take the distinction between persons adequately seriously. If a person remains miserable or painfully ill, her deprivation is not obliterated or remedied or overpowered simply by making someone else happier or healthier. Each person deserves consideration as a person, and this militates against a distribution-indifferent view" (Sen, 2001, p. 8). "More specific to utilitarianism, and closely related to its consequentialist structure, is the neglect of a person's *autonomy*. So – to a great extent – is the lack of interest in a person's integrity" (Sen and Williams, 1982, p. 5). Against this backdrop, Weyma Luebbe (2005) asked emphatically, "Have you ever sat at the deathbed of a statistical life?"

Second, the *aggregation problem* described by Norman Daniels (1993, p. 229) raises the question of whether (or when) small benefits for many can outweigh huge benefits for a small number of persons, as illustrated by the controversy surrounding the crooked teeth and thumb sucking rankings during the Oregon Health Plan experience.

Third, the *priorities problem* (Daniels, 1993, p. 228) concerns the severity of an initial health state as an expression of the dimension of the medical need for an intervention, i.e., the disregard of conventional CEAs for the severity of an illness as such. Only absolute QALY gains matter in CEA (Schwappach, 2002, Dolan and Olsen, 2002, Dolan et al., 2005, Schlander, 2005b). This means, following an example quoted by Klonschinski (2016, p. 97), "'that the benefit of providing ten

people with a utility gain of 0.1 for the rest of their life (corresponding to sildenafil treatment for men with erectile dysfunction) is […] equivalent to saving the life of a single (otherwise healthy) person.' (Schlander, 2008, p. 537)." In other words, the logic of cost effectiveness implies that all *QALYs* are treated equally, but it does not imply treating each *person* "as an equal" (Dworkin, 1977, p. 272). Klonschinski in her analysis concludes that, as "within utilitarianism, equality is specified as counting everyone's utilities equally. In doing so, it basically reduces persons to containers of utility and does not assign any primary normative relevance to their rights or liberties as such" (Klonschinski, 2016, p. 144, with reference to Sen and Williams, 1982, p. 4).

Fourth, empirically we know that many societies do not support fully utilitarian approaches. Citizens have been shown to adhere to *social norms* and hold social (or non-selfish) preferences beyond concerns for efficiency. This observation is consistent with the wide-spread belief that basic necessities "such as life, health and citizenship […] should be distributed less unequally than the ability to pay for them" – a view that has been referred to as "specific egalitarianism" (Tobin, 1970). As early as 1963, Kenneth Arrow noted "the concern of individuals for the health of others", which he "found in individual donations to hospitals and to medical education, as well as in the widely accepted responsibilities of government in this area." Arrow concluded that "the taste for improving the health of others is often stronger than for improving other aspects of their welfare" (ibid., p. 954).

Most people have preferences beyond narrow self-interest, for example, an interest in the social arrangements that shape the communities they live in. These "social preferences" include not only reciprocity (or "reciprocal fairness"), inequality aversion

and altruism, but also spiteful or envious preferences (Fehr and Fischbacher, 2002, 2003; Kurzban, 2015). The rapidly growing body of literature on social preferences clearly shows that the quasi-utilitarian "QALY *maximization* hypothesis" is not supported by a majority of citizens; rather, it was described as "descriptively flawed" in a systematic review of 64 experimental studies (Dolan et al., 2005).

Summing up, the ethical acceptability of CET-driven CEA hinges not only on the technical adequacy of the measurement metric itself, but likewise on the defensibility of the implied commitment to a particular decision rule. Consideration of social values beyond the "efficiency paradigm" inherent to the logic of cost effectiveness may require a departure from CET-based decision rules.

Social preferences other than "efficiency"

Well-documented social preferences include notably *equity concerns and a "sharing" perspective* (Richardson et al., 2012; Richardson and Schlander, 2018). Probably the best documented and least controversial attribute is the *severity of the initial health problem*. In empirical studies, people consistently showed a strong preference to prioritize health care for the worse off, and this priority has been found to be largely (although not totally) independent from the improvement achieved by an intervention, i.e., the difference between the pre- and post-intervention health state as captured by the conventional computation of incremental QALY gains (Ubel et al., 1996a; Nord, 1999; Ubel, 2000; Richardson and McKie, 2005, 2007; Shah, 2009; Linley and Hughes, 2013; Nord and Johansen, 2014; Khor

et al., 2023). Recognition of this has led to official HTA agencies making *ad hoc* adjustments of their CETs as a function of the severity of the initial health state (e.g., United Kingdom, Sweden, The Netherlands; cf. section below on "Real World Experience").

Another dimension of the severity of disease (and hence the "need" of patients, cf. below) are the broad *socioeconomic impacts* of serious disorders, including but not limited to many cancers, for patients, their caregivers and dependents (e.g., Shah et al., 2017; Inhestern et al., 2021), and other household members and relatives, triggered by loss of income and out-of-pocket costs (Schlander et al., 2024), with repercussions on health outcomes (Perrone et al., 2016; Ramsey et al., 2016) and quality of life (Jiang et al., 2023).

The problem of financial burden caused by serious disease has received surprisingly little attention in applied health economics, even though it is encountered not only in the United States, where the recognition of "financial toxicity" originated in 2013 (Zafar and Abernethy, 2013), but also in jurisdictions with universal health care and comprehensive social systems (Altice et al., 2016; Yabroff et al., 2016; Perrone et al., 2016; Yerramilli et al., 2018; Hernandez and Schlander, 2021; Ver Hoeve et al., 2021; Fitch et al., 2022; Schlander et al., 2024; Vancoppenolle et al., 2025).

There is some, albeit limited, empirical evidence that the public may not be prepared to deny patients treatment merely on the basis of *cost*. In an Australian two-stage survey, two equally effective interventions for two groups of patients were compared, the only difference between them being cost. Study participants (a cross-sectional sample of Australians generating 551 useable responses) were alerted to the fact that higher cost

of treatment would mean that fewer patients could be helped. Still, more than 80 percent of the respondents rejected cost as a relevant criterion when selecting a medical technology. Even when challenged by the researchers, highlighting the impact of the imposed budget limitation on the total number of patients receiving treatment, 70 percent preferred the equal priority option. When asked to explain their responses, survey participants "emphasized that people cannot be blamed for contracting high-cost illnesses, that severity of illness should count rather than cost, and that people were equally entitled to treatment irrespective to cost" (Nord et al., 1995).

Other studies reported essentially similar results, with high numbers of respondents rejecting allocation of resources on grounds of "health care opportunity costs" (Ubel et al., 1996b; Abellan-Perpinan and Pinto-Prades, 1999; Nord, 1999; Ubel, 2000; Bleichrodt et al., 2008; Blacksher et al., 2010; Desser et al., 2010; Richardson et al., 2012, 2018; Richardson and Schlander, 2018; and others). These findings indicate a strong social preference closely related to principles of fairness- or rights-based reasoning and inevitably constitute a serious challenge to the conventional logic of cost effectiveness and hence the use of CETs.

The studies cited here can all be categorized as high-quality choice-based stated preference analyses. Of course, in a methodologically less strict sense, one might feel tempted to also interpret the sensitivity of citizens to these issues – ranging from the public opposition to the cost-effectiveness-driven rankings of the OHP to the establishment of the Cancer Drugs Fund (CDF) in the UK – as revealed preferences pointing in the same direction.

Some further anomalies (reflective equilibrium issues)

There are many implications of CETs that have the potential to create dissonance between rankings based on CEA outcomes and widely held moral intuitions. In other words, they fail tests of wide reflective equilibrium (Rawls, 1971, p. 48; Daniels, 1979; Tersman, 1993; Knight, 2025). These tests imply that considered moral judgments about justice in particular cases should carry weight, and that failure to meet them cannot be simply done away as "irrational" because of conflicting with a particular theoretical result.

Three pertinent examples may suffice to illustrate the existence of reflective equilibrium issues in the present context:

(1) Effective *cancer* treatment often requires *combination therapy*; yet there are situations when adding an effective new drug to an established treatment regimen turns out to be "not cost-effective at zero price" (Latimer et al., 2021; also Fleeman et al., 2015; Danko et al., 2019) – with the resulting dilemma prompting a search for policy solutions, which led to the conclusion "that there is no one set of policies that is appropriate for all countries" (Henshall et al., 2023; p. 537).

(2) Next, studies of very *short-term benefits*, which translate in the gain of quality-adjusted life months (QALMs) or even quality-adjusted life days (QALDs) only, highlight issues associated with the assumed (almost, abstracting from the moderate effects of discounting) linear relationship between length of time and utility. In these studies, benefits accruing over a short time only are converted into QALYs by simple multiplication, for example with a factor of 12 or 365) in the case of QALMs or QALDs, respectively (Oh et al., 1996; Stadler et al., 2004; O'Connor et al., 2007; Meropol, 2008; Láinez, 2009; Hyle et al., 2020; Schuetz et

al., 2021; Sebastian et al., 2023; Chu et al., 2025; Kitano and Yoshida, 2025; Suzuki et al., 2025).

As an example of the potential implications, a CEA of an acute pain service showed that, when applying a standard CET of £30,000/QALY, the service would have to be considered inefficient if its (total) incremental cost exceeded £164, even if it (hypothetically) completely eliminated postoperative pain ''as severe as dead'' over two full days (with a health state utility weight u_0 = -0.2 compared to u_1 = 0.8) – irrespective of the fact that only a small number of patients would be affected and the budgetary impact at the system level therefore negligible (Stadler et al., 2004; Schlander, 2010).

By definition, the linearity assumption discussed above excludes any possibility of a diminishing marginal utility of remaining lifetime, with far-reaching implications also for the evaluation of end-of-life care, and potentially even the rule of rescue (Sinclair, 2022), in addition to the undervaluation of short-term testing and screening disutility (Swan et al., 2003, 2006, 2013), given the "likely result that the short-term state is trivialized" (Swan et al., 2013, p. 820).

(3) Finally, the *ranking of interventions* based on their cost effectiveness, which is asserted to reflect increasing social desirability with decreasing cost per QALY gained, is often presented as QALY (or cost effectiveness) "league tables" (Drummond et al., 1993; Mauskopf, 2003; and others). Yet the removal of tattoos (Drummond et al., 2007) or the prescription of sildenafil for the treatment of erectile dysfunction in elderly men suffering from diabetes (Skolk et al., 2000) would clearly meet the CET criterion, because in these cases strong *individual* preferences meet relatively low overall cost per patient. Conversely, interventions near the end of life (Trowman et al.,

2011; Schlander, 2010, 2024; Normand, 2012; Coast et al., 2021), including many cancer treatments, as well as interventions for people suffering from orphan diseases and for people in "double-jeopardy" (see below), rank at the lower end of the "league table", failing to meet commonly applied CETs.

The language of cost effectiveness does not even have terms capturing key aspects of palliative care beyond health maximization, such as respect for human dignity and autonomy, and its purpose to provide psychological, social and spiritual support, enabling a "good death" as the end of life comes closer, appreciating the individuality of death and dying (Normand, 2012; Yang and Mahon, 2012; Kinghorn and Coast, 2019; Krikorian et al., 2020; Coast et al., 2021; Schlander, 2024).

Consideration of ultra-rare disorders can only add to the cognitive dissonance caused by such rankings, as many enzyme replacement treatments for children with – in the absence of effective treatment – chronic debilitating genetic disorders are associated with ICERs (sometimes far) exceeding £100,000/QALY (Schlander and Beck, 2009; Schlander et al., 2014, 2016; Simonati and Williams, 2022; Charlton, 2022b; Moro et al., 2022).

Treating Persons:
Equality of QALYs or Equality of Patients?

The focus on treating actual patients as persons, its ethical significance and its collision with the utilitarian concentration on "maximizing the distribution-independent sum-total of utilities" (Sen, 2002, p. 662; cf. above), have been discussed in the literature primarily from a philosophical perspective and, in

particular, theories of justice (Rawls, 1971; Sen, 1980, 2001; Daniels, 2001, 2008; and others).

The correct use of a distribution-indifferent approach will necessarily, and "with some perversion" (in the words of Amartya Sen, 2002, p. 662), put already disadvantaged people, in particular those with disabilities and chronic illnesses, systematically "under a kind of double-jeopardy" (Singer et al., 1995). This is because co-existing conditions will inevitably reduce the potential to benefit from an intervention, i.e., the maximum quality of life (utility) weight that can be achieved; or conversely, multiple conditions require multiple simultaneous treatments to attain an improved health status (cf. Palladino et al., 2016; Makovski et al., 2019; Mueller et al., 2021), with implications for resource utilization and (again) incremental cost utility ratios. Already Sen emphasized specifically that "Rawls' criticism of the distribution indifference of utilitarianism (in not taking the difference between persons sufficiently seriously) would apply here with redoubled force" (Sen, 2002, pp. 662f.).

Likewise, Oregon's original waiver application for the OHP (cf. above; which was needed because it constituted a significant departure from the current Medicaid program) had been denied because the U.S. Department of Health and Human Services (HHS) reasoned that the OHP's reliance on cost effectiveness violated the Americans with Disabilities Act (ADA) of 1990 (cf. Kitzhaber, 2024).

Later, with the Patient Protection and Affordable Care Act (ACA) of 2010, Medicare and the newly formed Patient-Centered Outcomes Research Institute (PCORI) – with the mission to conduct comparative effectiveness research (CER) – were prohibited to use QALYs (or similar measures) "as a threshold to determine coverage, reimbursement, or incentive

programs" (Neumann and Weinstein, 2010, p. 1495). Only recently, with the House of Representatives passing the Protecting Health Care for All Patients Act (HR 485) of 2024, the prohibition for federal health programs to use of QALYs was again confirmed – despite assertions by some health economists that QALYs were "strongly egalitarian in their design," (according to the authors) a "feature […] summarized by a common refrain among those familiar with QALY methodology—'a QALY is a QALY is a QALY'"; Kaplan et al., 2024).

The empirical relevance of co-existing conditions

Still, the concern is that not only those unfortunate enough to be afflicted with high-cost illness, but also patients with disabilities or other severe co-existing conditions, including comorbidities, may face major obstacles to meet benchmarks of cost–effectiveness (Harris, 1987, 2005a,b; Singer et al., 1995; Nord, 1999; Ubel, 2000; Sen, 2002; Sinclair, 2011; Lavelle et al., 2018; Shields et al., 2022). The practical work-around-in applied CEA has been to simply ignore co-existing conditions and often also co-morbidities in CEAs and HTAs (Brown et al., 2005; Lavelle et al., 2018; Shields et al., 2022).

Despite the relevance of this common omission, it has been rarely discussed, with the usual defense resting on three grounds, (1) to avoid discrimination of the disabled, (2) because of violation of the Americans with Disabilities Act of 1990, and, additionally, (3) because of concern that ''an almost infinite number of cost-utility analyses [would be] required for just one intervention'' (Brown et al., 2005, pp. 163ff.). Yet, multi-

morbidity is highly prevalent, especially in medical inpatients. It is associated with poor healthcare outcomes and high costs of medical care.

Health care expenditures are well-known to be concentrated among a relatively small number of patients, in whom coexistence of multiple disorders is rather the rule than the exception (OECD, 2011; McDaid and Park, 2014; McPhail, 2016; Cortaredona and Ventelou, 2017; An et al., 2019; Nguyen et al., 2019; Soley-Borie et al., 2020; Holle et al., 2021; Marupuru and Axon, 2021; Mueller et al., 2021; Tran et al., 2022; Ho et al., 2022; Schiltz, 2022; Chowdhury et al., 2023; Niu et al., 2024; and many older ones, such as Alemayehu and Warner, 2004; Conwell and Cohen, 2005; Friedman et al., 2006, etc.). In the United States, for example, cross-sectional analyses of Medical Expenditure Panel Surveys (MEPS) show consistently that five percent of the population account for nearly half of the health care expenditures (Holle et al., 2021; Hernandez-Viver and Mitchell, 2024, 2025). In 2022, three out of four adults in the top-five (percentiles) expenditure tier had two or more "priority conditions" such as hypertension (42.9% compared to 18.7% in the overall sample, hyperlipidemia (35.6% vs. 14.6%), musculo-skeletal pain and back problems (30.6% vs. 12.2%), diabetes mellitus (25.6% vs. 7.9%), injuries (24.4% vs. 9.0%), anxiety (19.4% vs. 8.4%), cancer (18.3% vs. 5.3%), and arthritis (18.1% vs. 5.1%) (Hernandez-Viver and Mitchell, 2025).

Not least in the broader context of the patient-centered care movement (Coulter and Oldham, 2016; Catalyst NEJM, 2017; Calvert et al., 2019), it has been increasingly recognized that the value of health care should and can only adequately be characterized when grounded in the perspective of the actual patients with the disease (and their relatives, including caregivers). Indeed, the U.S. regulatory body, the Food & Drug

Administration (FDA), "increasingly looks to patients to understand how patients describe their health status, because patients are the experts in living with their disease or condition," and "[t]hey play a central role in ensuring that what matters to patients is factored into regulatory decision-making" (FDA, 2025).

Ira Wilson and Paul Cleary (1995) pointed out that the "clinical paradigm"– defined as "biomedical" model with the focus "on etiologic agents, pathological processes, and biological, physiological, and clinical outcomes" – needs to be differentiated from a broader "social science paradigm" – described as "quality-of-life" model, focusing "on dimensions of functioning and overall well-being" (Wilson and Cleary, 1995, pp. 59f.). The conceptual model of patient-reported outcomes (PROS, cf. US HHS/FDA, 2009; Grover et al., 2022) was refined by Jose Valderas and Jordi Alonso (2008) who also endorsed the central relevance of the patients' functional status, health perceptions, and health-related quality of life, emphasizing personal and environmental characteristics as outcome modifiers. More recently, calls were made to broaden the scope of CEAs to also consider the complex socioeconomic dimensions of disease from the perspective of patients and their relatives (Longo, 2023; Schlander et al., 2024).

The presence of co-existing conditions will impact both resource use and cost as well as PROs, even if defined less broadly. Since clinical decision-making is concerned with actual patients and the benefits conferred to (not *by*) them, the widely-followed convention to focus on single condition-treatment pairs (effectively must render the results of such CEAs as hypothetical data detached from the realities of clinical medicine. Many utility gains calculated on this basis will never be experienced by patients – and will therefore not accrue in real life (Harris

and Nease, 1997; Schlander, 2010; Assari et al., 2013; Husted et al., 2013; Adriaanse et al., 2016; Williams and Egede, 2016; Bahall et al., 2020; Gupta et al., 2021).

CETs and the ICER as Ratios

As a ratio, ICERs and consequentially CETs are, by their very definition, not influenced by the number of patients affected and therefore the dimension of a health care program. Since the number of patients appears both in the numerator as well as the denominator of the ratio, it cancels out.

Hence, ICERs (and CETs) do not differentiate between rare and wide-spread disorders, nor does do they offer policy-makers any hint concerning the budget impact or "affordability" of adopting a program. Authors of standard textbooks of health economics have admitted that indeed "[t]he largest criticism of ICER decision rules is related to the argument […] that ICERs only give us information about the cost per unit, not the total cost of the program," only to contend that "[w]ith perfect divisibility and constant returns to scale [note added: two 'technical characteristics' inherent in the computation algorithm, cf. Birch and Gafni, 1992] *this does not matter*" (Walker et al., 2011, p. 753).

Rare diseases and orphan medicinal products (OMPs)

Definitions of "orphan disorders" include a criterion of prevalence or incidence and differ somewhat between jurisdictions.

Official designation as an orphan medicine *further* requires that the product ("OMP") must meet additional criteria for the severity of the target disease and unmet medical need. For example, in the European Union it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically disabling, *and* that there either is no satisfactory intervention available, or (if such a method exists), the OMP must confer significant benefit to those affected by the condition (EMA, 2018).

Yet, many OMPs are unable to meet commonly applied CETs, which creates a serious mismatch between international policies to encourage and incentivize research and development (R&D) into, and patient access to, OMPs on the one hand, and the logic of cost effectiveness on the other hand (Schlander et al., 2014, 2016; Gammie et al., 2015; Postma et al., 2022).

From a cost perspective, this can be explained by the high fixed cost of orphan drug R&D (Jayasundara et al., 2019) in relation to small numbers of patients, often resulting in high drug acquisition costs per patient (Hughes-Wilson et al., 2012; Luzzatto et al., 2018; Korchagina et al., 2019; Althobaiti et al., 2023; Anderson, 2025; Hanchard, 2025; Mooney et al., 2025). Sometimes their use is associated with very high ICERs, even when OMPs offer higher health gains than non-orphan drugs (Chambers et al., 2020; Clifford et al., 2024).

Empirical studies across Europe indicated that positive coverage decisions are is less likely in jurisdictions that adopted the use of cost effectiveness as a key component of their HTA processes, such as England and Wales (HTA agency, National Institute for Health and Care Excellence, NICE) followed by Scotland (Scottish Medicines Consortium, SMC) and Sweden (Tandvårds- och läkemedelsförmånsverket, TLV), whereas agencies relying

on clinical value as their primary decision-making criterion – the French Haute Autorité de la Santé (HAS), the German Institute for Quality and Efficiency in Health Care (IQWiG), the Italian Agenzia Italiana del Farmaco (AIFA), and the Spanish Agency of Medicinal Products and Medical Devices (AEMPS) – were much more likely to recommend OMPs for reimbursement (Garau and Mestre-Ferrandiz, 2009; Zamora et al., 2019).

Even though a recent Canadian study (Ward et al., 2022) and research using sales data (Deticek et al., 2018) suggested a relatively better ranking of the UK, France and Germany remained consistently positioned at the top of the accessibility rankings based on indicators such as reimbursement (Garau and Mestre-Ferrandiz, 2009; Zamora, 2019] or market sales (Orofino et al., 2010; Picavet et al., 2012; Zamora et al., 2019).

From a value perspective, health economists have raised the question "should we value rarity?", and more specifically, "should we value the health gain to two individuals differently because one individual has a common disorder and the other has a rare disorder?" (McCabe et al., 2005, p. 1018). Other economists acknowledged that "[a] starting point for designing any health policy is to clarify society's views and objectives in relation to the issues concerned" only to assert that "the utilitarian perspective of maximising the total benefits to the population as a whole is a reasonable starting point" and to conclude that, "since orphan drugs are never as cost-effective as drugs for more prevalent diseases, departures from a strict utilitarian perspective [*note added*: meaning here CET-based decision-making] would have to be justified if they were to be funded" (Drummond and Towse, 2014, p. 335). The claim implies insistence on the principle of additive (linear) aggregation of individual utility into social value, requiring

strong assumptions about the mapping of individual WTP into social WTP (Smith and Richardson, 2005).

Other scholars invoked the relevance of institutional and legal context in support of providing access to orphan treatments even if not cost effective, including (1) human rights legislation, particularly Article 2 of the European Convention on Human Rights (ECHR), stipulating that 'everyone's right to life shall be protected by law'; (2) the United Nations Convention on the Rights of Persons with Disabilities; (3) EU disability legislation; and (4) in the UK, the Equality Act of 2010 and UK 'tort law' (Hyry et al., 2013; Schlander et al., 2014).

Empirical studies indicate a strong social preference of citizens to *not* disenfranchise patients with high-cost illness from access to treatment (Nord et al., 1995; Schwappach, 2002; Richardson et al., 2012, 2017, 2018; Richardson and Schlander, 2018), and an extensive debate has evolved about the normative and practical implications of policies to expand access to effective treatment options for rare diseases, and more recently, expensive Advanced Therapy Medicinal Products (ATMPs), such as cell- and gene-based therapies and tissue engineered products (for example, Isaacs, 2014; Kinney, 2014; Rhee, 2015; Juth, 2017; Rodriguez-Monguio, 2017; Gennet, 2020; Juth et al., 2021; Zimmermann et al., 2021; Rejon-Parrilla et al., 2023; Alam et al., 2025; Hanchard, 2025; Vargas et al., 2025; Spacirova et al., 2026). The orthodox logic of cost effectiveness relying on CETs has contributed next-to-nothing to this ongoing debate.

IV

Budget impact and "affordability"

One of the most obvious challenges to the credibility of the ICER-based logic of cost effectiveness as a decision-making framework is its silence on the budgetary impact of an intervention (Birch and Gafni, 1992; 2006a; Gafni and Birch, 1993, 2006) – reflecting the notion of "affordability" from a policy-maker's perspective. Senior NICE representatives asserted that they cannot know about the net budget impact of NICE guidance as there is no counterfactual, i.e., no information about how NHS expenditures would have developed in the absence of NICE guidance. The nonavailability of relevant data was further complicated by the fact that the NHS budget more than doubled in real terms between 1999 and 2010, whereas the NICE CET was not adjusted until very recently (Appleby, 2016, pp. 166f.). NICE has further insisted repeatedly that considerations of "affordability" were not a part of NICE technology appraisals (Rawlins and Culyer, 2004, p. 225; Pearson and Rawlins, 2005, p. 2619); rather, budget impact estimates were produced initially for the sole purpose of supporting regional fundholding authorities who are mandated to implement NICE guidance (NICE, 2005; Barnes et al., 2007; Chidgey et al., 2007; Ogden, 2017a,b). As observed early by Alan Williams and others (e.g., Birch and Gafni, 2006b), this insistence was in stark contrast with "the fact that such [affordability] considerations are the only justification there is for having a benchmark!" (Williams, 2004, p. 8) – an inconsistency (i.e., a serious narrow equilibrium issue) permeating the logic of cost effectiveness from the beginning. Under the fixed budget approach of the tax-funded NHS, this caused debate about the (unknown) programs that would be displaced by the new ones recommended by NICE (McCabe et

al., 2008; Hughes and Ferner, 2010; Garner and Littlejohns, 2011; Hughes, 2015; Charlton, 2020, 2024; Charlton et al., 2022; and others). At the same time products such as hepatitis C medicines were deemed cost effective by both NICE and other international HTA agencies, but then delayed in adoption by the healthcare system (i.e., in England the NHS) due to budget limitations (Kamal-Yanni, 2015; Iyengaar et al., 2016; Timmins et al., 2017, pp. 127f.; Shetty et al., 2024). -

As a consequence, NICE and the NHS England introduced another adjustment, an additional annual budget impact threshold (BIT) in April 2017. New drugs that have a net impact of £20 million or more in any of their first three years of use trigger commercial negotiations between NHS England and the drug manufacturer, with the goal of mitigating the affordability challenge for the NHS England. Following controversial debate, the BIT was increased to £40 million effective as of April 2026 (NHS England, 2024; Robertson, 2025a,b). Exceeding the BIT will require price negotiations, which add to the cost effectiveness hurdle (the upwardly revised CET as of April 2026) and the Voluntary Scheme for Branded Medicines Pricing, Access and Growth (VPAG) regulation, matters of continuing debate in the UK (Robertson, 2025b, 2026; Science Media Centre, 2025; Cookson et al., 2026).

In the context of CETs, it is easy to see that any additional budget impact criterion must create an inconsistency with the conventional logic of cost effectiveness, i.e., a narrow reflective equilibrium problem, and it has been critiqued by British health economists as an "unpopular and flawed attempt to solve a fundamentally political problem" that can be likened to "seeking to square the circle" (Charlton et al., 2017), undermining NICE's stated commitment to an "ethics of opportunity costs" (Rawlins, 2004, p. 578; Rawlins and Culyer,

2004; Rid et al., 2015; Charlton et al., 2017; Rumbold et al., 2017; Charlton, 2020).

As explicated earlier, an ethics of health opportunity costs rests on the questionable assumption that QALYs in fact capture the full value of health and health care. Affordability concerns have, however, always been relevant in the context of health care priority-setting, are cited in many textbooks as central motivation to turn to economic evaluation, and are reflected by the prevalent use of budget impact criteria in many jurisdictions including Australia and Canada (Pichon-Riviere et al., 2025).

Real World Observations

Criticisms and public debate have long surrounded the impact of CEA and CETs on access to medicines for patients. For example, a public outcry challenged NICE's HTA process with its reliance on cost effectiveness not only because of negative recommendations for a number of new medicines, famously including the case of the parallel assessment of four new drugs for advanced renal cell cancer. Rather, the time needed by NICE to produce a final appraisal determination played a critical role, as "new products were being held up for too long while NICE studied them and the NHS refused to fund them" (Timmins, 2017, p. 78). NICE had decided to defer looking at the first product until all four would be available, and to evaluate them as a group. In addition to the resulting delay of nearly two years until the appraisal of the first product would begin (Timmins, 2009, p. 1363), the assessment itself gave rise to heated controversy, as all four treatments were found clinically effective but not cost effective, with ICERs estimated between

£71,462 and £171,301 per QALY gained (Chang, 2018). When negative draft guidance was published in August 2008, stakeholders disagreed almost unanimously with NICE's recommendations. Most comments were concerned with the reliability of the economic model used by the technology assessment group, the appropriateness of the NICE evaluation methodology including its reliance on the QALY as a measure of outcomes, and the implications for equal access to effective treatment (Chang, 2018). One year later, in 2009, NICE reversed its negative decision on one out of the four treatment options for renal cell cancer, following the extension to its CET for "end-of-life" treatments (Timmins et al., 2017; Chang, 2018).

Delayed access due to prolonged HTA processes

As an observation aside from the CET subject, it can be noted here that HTA processes (with or without CEAs) are not only resource-intense, but may result in delayed access to new treatments, even if effective (and cost effective). NICE reacted by introducing its Single Technology Appraisal (STA) process in 2005, and by fast-tracking its review of trastuzumab, resulting in a positive recommendation within less than a month after its license for use in early-stage breast cancer in 2006 (Timmins, 2017, pp. 75ff.). The STA process itself was amended by a Fast Track Appraisal (FTA) process from April 2017 to February 2022, open for technologies considered to offer exceptional value for money (i.e., base case ICERs below 10,000 £/QALY). It was replaced in 2022 by a cost comparison "proportionate" approach to speed up FTAs (Kaltenthaler et al., 2011; Bresnahan et al., 2023; NICE, 2023, 2026).

Comparable issues arose elsewhere, too. For example, the national Canadian HTA agency (CDA-AMC) introduced a new "Time-Limited Recommendation" (TLR) category to reduce the total time from regulatory approval to provincial listing of oncology drugs exceeding 500 days. TLR has been accompanied by a temporary access process, essentially a path to conditional reimbursement similar to coverage with evidence development schemes in other jurisdictions (Glennie et al., 2022; Cowling et al., 2023).

Threshold adjustments

To address concerns over reduced or delayed access as a result of rigid cost-effectiveness thresholds, not only a series of modifications of funding pathways but also alternative thresholds have been implemented. In the UK, *"end-of-life" (EoL) guidance* was introduced by NICE in 2009. The EoL guidance implied an additional weight of up to a maximum of 1.7 or approximately £50,000 per QALY gained (Bovenberg et al., 2021), providing the technology of interest was indicated for a condition associated with a life expectancy of less than two years, and extended life by at least three months compared to standard treatment in the NHS. A third requirement, a "small target population", was added originally but was lifted again in 2016. In effect, the EoL criterion led to a higher CET almost exclusively for drugs to treat late-stage cancers (Bovenberg et al., 2021). In February 2022, NICE replaced the EOL guidance with a "*severity modifier*," introduced to provide additional weighting to some medicines that treat more severe conditions (Angelis et al., 2023; NICE, 2024a,b). According to a study

analyzing the eligibility for higher QALY weighting, based on technology appraisals between January 2020 and December 2022, higher QALY weights will be harder to achieve under NICE's severity modifier compared to the EoL criteria (Njoroge et al., 2024).

Different from the quantitative qualifier for OMPs, which in the EU and in the UK has been set at a prevalence rate of fewer than 1 in 2,000 people, NICE defined a subcategory of ultra-rare diseases (URDs) to require a prevalence of less than 1 in 50,000, or less than 1,000 people in England and Wales (Abozaid et al., 2025). Only OMPs fulfilling restrictive additional criteria fall under the exceptional process for URDs; all other rare disease technologies are subject to NICE's standard single technology appraisal (STA) route, including application of its traditional cost effectiveness threshold of up to £30,000 per QALY gained (or £36,000 or £50,000 per QALY, respectively, if and when the criteria for application of NICE's severity modifier are met).

For URDs, however, NICE inaugurated a separate appraisal subsystem in 2013, known as the "Highly Specialised Technology" (HST) program. The eligibility or "routing" criteria are highly restrictive and were last refined effective April 1, 2025 (NICE, 2025). If all criteria have been met, NICE will apply an alternative CET, ranging from £100,000 up to £300,000 per QALY gained, much higher than its usual CET. In the HST process, the lower bound of the CET, set at £100,000 / QALY, will be increased as a function of the therapeutic improvement. For example, a QALY gain of 20 would be assigned a weight of 2, resulting in an applicable CET of £200,000 / QALY. The *rationale* offered by NICE is remarkable as it implies an explicit distancing from an "efficiency-only" approach (as it is underlying the public health maximization hypothesis and derived calculus of CETs), giving priority to fairness-related con-

siderations: "Given the very small numbers of patients living with these very rare conditions a simple utilitarian approach, in which the greatest gain for the greatest number is valued highly, is unlikely to produce guidance which would recognise the particular circumstances of these very rare conditions. These circumstances include the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for companies in making a reasonable return on their research and development investment because of the very small populations treated. Nevertheless, as part of its consideration of the value for money of the technology, the committee must give consideration to the balance between the costs and the benefits" (NICE, 2017, pp. 7f.).

Still, the very stringent criteria for routing drugs into the HST process constitute a remarkably restrictive bottleneck, with the consequence that most OMPs continue to face substantial challenges to obtain a positive recommendation under NICE's standard single technology appraisal (STA) process (Lee et al., 2023; Hale et al., 2023). Of note, both the narrow eligibility criteria of the HST process (Upadhyaya, 2025) as well as the modified threshold (Charlton, 2022b) have been critiqued for being arbitrary and difficult to justify.

Alternative access programs for non-CE treatments have been attempted

Almost in parallel to the development of EoL guidance by NICE, a *Cancer Drugs Fund (CDF)* was created in the UK, initially endowed with an annual budget of £200 million "ring-

fenced" for subsidizing the use of anticancer medicines otherwise not available within the NHS. Preceded by an *Interim Cancer Drugs Fund* from October 2010 to March 2011, the CDF became operational in April 2011, intended to be a temporary fix until a value-based pricing (VBP) system would have been established in the NHS, which was hoped to broaden the scope of NICE's approach to incorporate further elements of value and thus increase the acceptance rate of cancer drugs on grounds of their cost effectiveness. In the meantime, the CDF was to improve patient access to new cancer medicines, which were not recommended by NICE for reasons of cost effectiveness (Timmins et al., 2017; Morrell et al., 2018).

The CDF soon exceeded its allocated budget, with annual expenditures growing to £466 million in 2015-2016, an increase of £126m or 37% over its allocated budget of 340 million in 2015-2016 – even though in the interim two re-prioritization exercises had been undertaken (Morrell et al., 2018; Lewison et al., 2018). After extensive debate, the CDF was reconfigured in 2016 and works now as a managed access scheme under the umbrella of NICE.

There are further international examples. For instance, a *Life Saving Drugs Programme* (LSDP) was introduced in Australia in 1995 for high-cost transformational therapies for rare diseases to cover medicines that fail to meet standard expectations for cost effectiveness. It is restricted to clinically effective (but not "cost effective") medicines to life-threatening ultra-rare conditions (defined as 1 case per 50,000 or fewer in the Australian population). In Canada, much debate has focused on the impacts of the CAN-$ 50,000 threshold and the complex approval and price negotiation process on timely access of new drugs, especially for treatment of cancers and some rare disorders (cf. Adkins et al., 2017; Salek et al., 2019; Rawson,

2022), especially in light of the absence of specific criteria for orphan medicinal products (OMPs) in Canada (Rawson, 2022; Ward et al., 2022).

Conclusions

Choices and prioritization are inherent in any health system, but the use of conventional cost effectiveness analyses (CEAs) – with quality-adjusted life years (QALYs) as their presumably universal and comprehensive measure, capturing the value ("*utility*") conferred by health and health care – is not the only way to make these inherently normative choices.

The selection of the most appropriate approach for a given country should be guided by its alignment with local values, objectives, and institutional context. If interpersonal equity ranks high among the objectives of a health system, this will necessarily lead to caution regarding the logic of cost effectiveness and any application of universal cost effectiveness thresholds (CETs). Fair allocation of health care resources to persons – or the chance of access to effective treatment for patients – will put nondiscrimination (among the prime examples, patients with rare disorders) and distributive justice high on the agenda, consistent with the dominant view of collectively financed health schemes as social institutions. The widely held belief that basic necessities "such as life, health and citizenship […] should be distributed [between persons] less unequally than the ability to pay for them" – a view that has been referred to as "specific egalitarianism" (Tobin, 1970) – contradicts claims of so called "QALY egalitarianism" (Culyer, 1992), given their potential discriminatory consequences for all

those unfortunate enough to suffer from a rare, severe, urgent, or high-cost health problem. Still, CEAs are used to inform health care resource allocation decisions in many jurisdictions in the context of Health Technology Assessments (HTAs). For CEAs to be useful, a benchmark or "cut-off" level is needed separating cost effective from not cost effective interventions – here referred to as CET. There is, however, persistent controversial debate not only about the appropriate size of CETs, but also the appropriateness of universal CETs as a measure of the implicit or explicit willingness-to-pay (WTP) for expected health gains as such.

In principle, health economic theory permits to derive the size of a potential CET from observed preferences ("demand-side perspective") or from an "health opportunity cost" (or "supply-side") perspective. Adopting a demand-side perspective consistently results in much higher CET estimates than supply-side models (e.g., Vallejo-Torres et al., 2016); it is further complicated by methodological choices and the wide variation of values of a "statistical life (year)" reported in the empirical economic literature. On the other hand, supply-side models of the "shadow price" of a QALY rest on many assumptions, most notably the claims that the QALY construct captures the complete value conferred by health care, and that the (sole) objective of the health scheme in question ought to be the maximization of QALYs produced.

The quasi-utilitarian QALY aggregation principle is highly problematic from an ethical perspective, as it reduces patients to containers of QALYs and "does not assign any primary normative relevance to their rights and liberties as such" (Klonschinski, 2016, p. 144; Sen and Williams, 1982, p. 4). More than this, empirical research has shown that the maximization assumption is "descriptively flawed" (e.g., Dolan et al., 2005);

citizens have been found to adhere to social norms and hold social (i.e., non-selfish) preferences, in particular in health care contexts (Arrow, 1963, p. 954; Tobin, 1970; Fehr and Fischbacher 2002, 2003; Kurzban, 2015). The maximization hypothesis fundamentally collides with the character of collectively financed health schemes as social institutions, with objectives beyond – and different from – the maximization of a construct of population health such as the sum of QALYs produced.

The real-world relevance of these considerations is illustrated by counterintuitive cost per QALY rankings – according to the cost effectiveness paradigm, coverage of tattoo removals or of sildenafil treatment for erectile dysfunction in elderly diabetics ought to be much more socially desirable than, for example, funding of many cancer treatments and enzyme replacement therapies for children with debilitating hereditary lysosomal storage diseases (Drummond et al., 2007; Stolk et al., 2000a,b; Schlander et al., 2014, 2016; Simonati and Williams, 2022; Charlton, 2022b; Moro et al., 2022).

The problem is aggravated by further deficiencies of a presumably "technical nature", in particular the character of CETs as incremental cost effectiveness ratios (ICERs), which by their very definition are blind to the dimension of the health care programs evaluated, i.e., both to the number of persons affected and to their budgetary impact (e.g., Birch and Gafni, 1996). Likewise, the convention widely held among health economists to analyze condition-treatment pairs without consideration of co-existing conditions fails to consider the concentration of disease (comorbidities and co-existing disorders) and cost among small numbers of patients. While it might serve to circumvent the hotly debated ethical issue of discrimination against people in "double-jeopardy", such as the disabled and chronically ill, it does so at the expense of

calculating hypothetical costs per QALY gained that will be unattainable in many real-world patients. These (and further) assumptions may explain results of CEAs that are inconsistent with strong moral intuitions, giving rise to serious wide reflective equilibrium issues, including but not limited to rule of rescue situations, the wish to prioritize care for persons in high need and urgent conditions, and non-discrimination against patients with rare diseases.

These issues have led some HTA agencies that pioneered the use of CEA and CETs, most notably the UK National Institute for Health and Care Excellence (NICE), to cautiously begin abandoning key principles of the underlying logic by introducing CET adjustments for severity and for (ultra-) rare disorders. NICE has been praised as "the closest anyone has yet come to fulfilling the economist's dream of how priority-setting in health care should be conducted" by Alan Williams (2004, p. 3), who at the same time insisted that "[affordability] considerations are the only justification there is for having a benchmark!" (ibid., p. 8). Remarkably, the foundation chairman of NICE admitted that utilitarian approaches offer "nothing to the eradication of health inequalities" (Rawlins, 2015, p. 215) and "can sit uncomfortably with the desire to ensure fairness […]" (Rawlins, 2004, p. 578), while at the same time insisting on the proverbial claim that "a QALY is a QALY is a QALY" (Rawlins and Culyer, 2004, p. 226).

Yet perhaps the most striking departure from the logic has been the introduction of budget impact thresholds by some agencies, again including NICE (Pichon-Riviere et al., 2025), in response to the silence of CETs about the dimension (i.e., the "affordability") of the health care programs under evaluation. Each of these modifications, which were introduced by agencies after careful consideration only, (and even more so all of them

taken together,) result inevitably in substantial coherence problems between "theory […,] priority-setting policy and practice" (Charlton and DiStefano, 2024). They illustrate the failure of the logic of cost effectiveness (and hence CETs) as a universal paradigm for health care priority setting and must cast doubt on the reliability of the framework, ultimately calling into question its status as a valid scientific theory.

The internal inconsistencies (or "narrow reflective equilibrium issues") resulting from the actual deviations from the underlying logic are indicative of the technocratic ("or "political") nature of CETs, which became most visible by the conspicuous adjustment to its standard CET recently made by NICE under external pressure. The purpose of the CET had been rationalized earlier by one of its most influential proponents "to keep matters [*added*: meaning rising NHS expenditures] in check for a while," suggesting that "it would be better to err on the side of caution and apply a lower threshold" (Williams, 2004, p. 14). Given the absence of a robust scientific grounding of CETs in the first place, one might feel tempted to ask about the rationale for the numeric values of the CET modifiers now applied – even more so, as both severity and rarity represent continuous phenomena and not separate categories, as implied by the restrictive qualifiers for their use – such as the "routing criteria" for the *Highly Specialised Technology* appraisal process within NICE. Observers close to NICE revealed the extent that NICE reacted to external pressures in attempts to avoid political storms (see Timmins et al., 2017, and Atkinson and Sheard, 2025).

Adding to these anomalies, there is a growing discontent about the apparent inability of CEA and CETs to adequately address the economic challenges posed by many new innovative medicines, including cancer treatments and their combinations,

by Advanced Therapy Medicinal Products (ATMPs), innovative gene-, cell- or tissue-based therapies;,and, of course, by Orphan Medicinal Products (OMPs), while at the same time allowing some "cost effective" therapies for wide-spread diseases to potentially break the system.

Finally, it seems noteworthy to emphasize that in standard CEAs, health gains ("effectiveness") are conceptualized as life years gained (LYGs) or, more commonly, quality-adjusted life years (QALYs) gained. Using a specific algorithm, QALYs combine probability of occurrence ("risk"), length and quality of life in a single index, assumed to capture the full value of a health state on a cardinal scale. Essentially, QALYs are calculated according to a simplistic aggregation formula, allowing for analytical convenience while effectively excluding other combinations of these attributes as well as other potential sources of value. Not only in the academic sphere, but also among HTA agencies working with CEA and CETs, there are signs of an increasing recognition of health care benefits beyond – and likely apart from – the efficient production of QALYs (Al-Janabi et al., 2016; Schlander et al., 2016; Lakdawalla et al., 2018; Richardson and Schlander, 2018; Brouwer, 2019; Drummond et al., 2020; Brouwer and van Baal, 2023; Longo, 2023; McQueen et al., 2026; Radu et al., 2026), so there is reason for hope that future developments may lead to less restrictive benefit functions for use in HTAs.

Summing up, the omission of specific benefits is not a neutral position, as it cannot increase fairness but serves only to making those benefits unobserved. Further to this, it is important to realize that expanding a benefit function or broadening the perspective of analysis does not necessarily imply making funding decisions more permissive (cf. Steuten, 2026). International health care policy makers would thus seem well-

advised to exercise caution in adopting the logic of cost effectiveness thresholds in decision-making, whereas health economists might be expected to prioritize the exploration of potential alternatives to the conventional logic, which should better incorporate the social dimension of health care.

Afterword

For reasons of scope and size (wordcount, length of text), the present essay-style narrative review presents a massively shortened version of work in progress; for example, the cited literature has been cut by more than two thirds in the down-sizing process. The present version also does not provide a critical discussion of the most promising ways forward. These will be subject of subsequent work, hopefully with contributions by many scholars.

In the meantime, if we are prepared to accept that "health equity is inescapably multidimensional as a concern" (as observed by Amartya Sen and others), we might be well advised to also accept (at least as long as we are searching for a better priority-setting paradigm) that it may be "far better [to seek] an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can be made precise" (a quote attributed to John W. Tukey).

Unless better health economic approaches are developed, a more holistic approach, such as some variant of multi-criteria decision analysis (MCDA), might offer a transparent framework serving as an interim solution that is more pragmatic and more flexible for alignment with local needs, institutional context, values and health system structure in a given jurisdiction.

IV

References

- Aaron H. (1995). *The Problem That Won't Go Away: Reforming U.S. Health Care Financing*. Washington, D.C.: Brookings Institution Press.
- Abellan-Perpiñán, J.M., Pinto Prades, J.L. (1999). Health state after treatment: a reason for discrimination? *Health Economics*, 8 (8): 701–707.
- Abozaid, G.M., Kerr, K., Alomary, H., Al-Omar, H.A., McKnight, A. (2025). Global insight into rare disease and orphan drug definitions: a systematic literature review. *BMJ Open*, 15: e086527; doi: 10.11.36/bmjopen-2024-086527.
- ABPI (2025). *Why the government must urgently raise the NICE cost-effectiveness threshold*. London, England: Association of the British Pharmaceutical Industry (ABPI), 07 October 2025, posted in blog by Victoria Jordan. https://www.abpi.org.uk/media/blogs/2025/october/why-the-government-must-urgently-raise-the-nice-cost-effectiveness-threshold; last accessed December 19, 2025.
- Adkins, E.M., Nicholson, L., Floyd, D., Ratcliffe, M., Chevrou-Severac, H. (2017). Oncology drugs for orphan indications: how are HTA processes evolving for this specific drug category? *ClinicoEconomics and Outcomes Research*, 9: 327-342.
- Adriaanse, S.M., Drewes, H.W., van der Heide, I., Struijs, J.N., Baan, C.A. (2016). The impact of comorbid chronic conditions on quality of life in type 2 diabetes patients. *Quality of Life Research*, 25 (1): 175-182.
- Akehurst, R.L., Abadie, E., Renaudin, N., Sarkozy, F. (2017). Variation in Health Technology Assessment and

Reimbursement Processes in Europe. *Value in Health*, *20* (1): 67–76.

- Alemayehu, B., Warner, K.E. (2004). The lifetime distribution of health care costs. *Health Serv Res*., 39 (3): 627-662.
- Al-Janabi, H., van Exel, J., Brouwer, W., Coast, J. (2016). A framework for including family health spillovers in economic evaluation. *Medical Decision Making*, 36 (2): 176-186.
- Al-Jedai, A.H., Lomas, J., Almudaiheem, H.Y., Al-Ruthia, Y.S.H., Alghamdi, S., Awad, N., Alghamdi, A., Alowairdhi, M.A., Alabdulkarim, H., Almadi, M., Bunyan, R.F., Ochalek, J. (2023). Informing a cost-effectiveness threshold for Saudi Arabia. *Journal of Medical Economics*, 26 (1): 128-138.
- Alam, E.U., Ekpang Ii, J.E., Ekpang, P.O., Ainebyoona, C., Nwagu, K.E., Nwuruku, O.A., Muhammad, K. (2025). Toward an ethical future for orphan drugs: balancing access, affordability, and innovation. *Journal of Medical Economics*, 28 (1): 1869-1886.
- Allen, N., Walker, S.R., Liberti, L., Salek, S. (2017). Health Technology Assessment (HTA) Case Studies: Factors Influencing Divergent HTA Reimbursement Recommendations in Australia, Canada, England, and Scotland. *Value in Health*, 20 (3): 320-328.
- Altice, C.K., Banegas, M.P., Tucker-Seeley, R.D., Yabroff, K.R. (2016). Financial hardships experienced by cancer survivors: a systematic review. *Journal of the National Cancer Institute*, 109 (2): djw205.
- Althobaiti, H., Seoane-Vazquez, E., Brown, L.M., Fleming, M., Rodriguez-Monguio, R. (2023). Disentangling the cost of orphan drugs marketed in the United States. *Healthcare*, 11: 558.

- Altman, S.H., Tompkins, C.P., Eilat, E., Glavin, M.P.V. (2003). Escalating health care spending: is it desirable or inevitable? *Health Affairs (Millwood)*, 22 (Suppl. 1): Web Exclusive; *https://doi.org/10.1377/hlthaff.W3.1*.
- An, J., Nyarko, E., Hamad, M.A. (2019). Prevalence of comorbidities and their associations with health-related quality of life and healthcare expenditures in patients with rheumatoid arthritis. *Clinical Rheumatology*, 38 (10): 2717–2726.
- Anand, P. Dolan, P. (2005). Equity, capabilities and health. *Social Science & Medicine*, 60 (2): 219-222.
- Andersen T. M. (2016). Does the public sector implode from Baumol's cost disease? *Economic Inquiry*, 54 (2): 810-818.
- Anderson L.-A. (2025). *10 of the most expensive drugs in the U.S.* Drugs.com. *https://www.drugs.com/article/top-10-most-expensive-drugs.html*. Last updated on November 19, 2025; last accessed on November 25, 2025.
- Angelis, A., Lange, A., Kanavos, P. (2018). Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. *European Journal of Health Economics*, 19: 123-152.
- Angelis, A., Harker, M., Cairns, J., Seo, M. K., Legood, R., Miners, A., Wiseman, V., Chalkidou, K., Grieve, R., Briggs, A. (2023). The Evolving Nature of Health Technology Assessment: A Critical Appraisal of NICE's New Methods Manual. *Value in Health*, *26*(10): 1503–1509.
- Annemans L. (2008). *Health economics for non-economists. An introduction to the concepts, methods and pitfalls of health economic evaluations*. Gent: Academia Press.

- Appleby, J., Devlin, N., Parkin, D., Buxton, M., Chalkidou, K. (2009). Searching for cost effectiveness thresholds in the NHS. *Health Policy*, 91 (3): 239–245.
- Appleby J. (2016). Crossing the line: NICE's value for money threshold. *British Medical Journal,* 352: i1336.
- Appleby J. (2017). What's In and What's Out? The Thorny Issue of the Threshold. In: Timmins, N., Rawlins, M., Appleby, J. (eds.) *A Terrible Beauty: A Short History of NICE - The National Institute for Health and Care Excellence*. Muang, Thailand: Amarin Printing and Publishing Co., Ltd.
- Arrow K.J. (1963). Uncertainty and the welfare economics of medical care. *The American Economic Review*, 53 (5): 941-973.
- Assari, S., Lankarani, M.M., Ahmadi, K. (2013). Comorbidity influences multiple aspects of well-being of patients with ischemic heart disease. *International Cardiovascular Research Journal*, 7 (4): 118-123.
- Australian Government Department of Health (2016). *Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee*. Version 5.0, September 2016. Canberra, ACT: Commonwealth of Australia represented by the Department of Health.
- Australian Government Department of Health and Aged Care (2025). About the Life Saving Drugs Program. *https://www.health.gov.au/our-work/life-saving-drugs-program/about-the-lsdp*; last accessed May 02, 2025.
- Bahall, M., Legall, G., Khan, K. (2020). Quality of life among patients with cardiac disease: the impact of comorbid depression. *Health and Quality of Life Outcomes*, 18 (1): 189.
- Bala, M., Zarkin, G.A., Mauskopf, J.A. (2002). Conditions for the near equivalence of cost-effectiveness and cost-benefit analyses. *Value in Health*, 5 (4): 338-346.

- Balijepalli, C., Gullapalli, L., Joshy, J., Rawson, N.S.B. (2024). The impact of willingness-to-pay threshold on price reduction recommendations for oncology drugs: a review of assessments conducted by the Canadian Agency for Drugs and Technologies in Health. *Journal of Comparative Effectiveness Research*, e230178.
- Barnes, S., Leng, G., Bent, N., Campbell, B. (2007). Implementation support for NICE guidance. *Annals of the Royal College of Surgeons of England*, 89 (5): 542-543.
- Barnsley, P., Towse, A., Karlsberg Schaffer, S., Sussex, J. (2013). *Critique of CHE Research Paper 81: Methods for the Estimation of the NICE Cost Effectiveness Threshold*. London: Office of Health Economics, Occasional Paper 13/01, December 2013.
- Bartol, A., Dressler, K., Kaskel, P., Landsberg, C., Lechner, C., Petschulies, M. (2023). Ten years of AMNOG from an oncolocgical perspective: new horizons and continuing expansion. *Journal of Cancer Research and Clinical Oncology*, 149: 2637-2645.
- Baumol W.J. (2012). *The cost disease. Why computers get cheaper and health care doesn't*. New Haven, CT: Yale University Press.
- Beauchamp, T.L., Childress, J.F. (1979). *Principles of Biomedical Ethics*. Oxford: Oxford University Press.
- Bentham J. (1824). An introduction to the principles of morals and legislation. In: Mill, J.S., Bentham, J. (Editors) *Utilitarianism and Other Essays*. Harmandsworth: Penguin 1987.
- Bertram, M.Y., Lauer, J.A., De Joncheere, K., Edejer, T., Hutubessy, R., Kieny, M.P., Hill, S.R. (2016). Cost-effectiveness thresholds: pros and cons. *Bulletin of the World Health Organization*, *94* (12), 925–930.

- Bertram, M.Y., Lauer, J.A., Stenberg, K., Edejer, T.T.T. (2021). Methods for the economic evaluation of health care interventions for priority setting in the health system: an update from WHO-CHOICE. *International Journal of Health Policy Management*, 10 (11): 673-677.
- Binder, L., Ghadban, M., Sit, C., Barnard, K. (2022). Health Technology Assessment Process for Oncology Drugs: Impact of CADTH Changes on Public Payer Reimbursement Recommendations. *Current Oncology*, 29: 1514-1526.
- Birch, S., Gafni, A. (1992). Cost–Effectiveness/Utility Analysis: Do Current Decision Rules Lead us to Where We Want to be? *Journal of Health Economics*, 11: 279–296.
- Birch, S., Gafni, A. (1993). Changing the problem to fit the solution: Johannesson and Weinstein's (mis)application of economics to real world problems. *Journal of Health Economics* 12: 469-476.
- Birch, S., Gafni, A. (2006a). Information created to evade reality (ICER): things we should not look to for answers. *Pharmacoeconomics,* 24 (11): 1121-1131.
- Birch, S., Gafni, A. (2006b). Decision rules in economic evaluation. In: Jones, A.M. (editor) *The Elgar Companion to Health Economics*. Cheltenham: Edward Elgar, 492-502.
- Blacksher, E., Rigby, E., Espey, C. (2010). Public values, health inequality, and alternative notions of a "fair" response. *Journal of Health Politics, Policy and Law*, 35 (6): 889–920.
- Bleichrodt, H., Crainich, D., Eeckhoudt, L. (2008). Aversion to health inequalities and priority setting in health care. *Journal of Health Economics*, 27 (6): 1594–1604.
- Blome, C., Augustin, M., Metin, H., Lohrberg, D. (2017). Four years of early benefit assessment of new drugs in Germany: a qualitative study on methodological

requirements for quality of life data. *European Journal of Health Economics*, 18: 181-193.

- Bobinac, A. Van Exel, NB.J., Rutten, F.F., Brouwer, W.B. (2010). Willingness to pay for a quality-adjusted life-year: the individual perspective. *Value in Health*, 13 (8): 1046-1055.
- Bouvy J. (2024). *Should NICE's cost-effectiveness thresholds change?* London, National Institute for Health and Care Excellence (NICE). Blog, December 13, 2024. *https://www.nice.org.uk/news/blogs/should-nice-s-cost-effectiveness-thresholds-change-*; last accessed January 12, 2026.
- Bovenberg, J., Penton, H., Buyukkaramikli, N. (2021). 10 Years of End-of-Life Criteria in the United Kingdom. *Value in Health*, 24 (5): 691-698.
- Brent R.J. (2003). *Cost-Benefit Analysis and Health Care Evaluations*. Cheltenham, Edward Elgar.
- Bresnahan, R., Houten, R., Greenhalgh, J., Nevitt, S., Mahon, J., Beale, S., Boland, A., Bhattacharyya, D., Dundar, Y., McEntee, J., Gandhi, S., Fleeman, N., Chaplin, M. (2023). Pegcetacoplan for Treating Paroxysmal Nocturnal Haemoglobinuria: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *PharmacoEconomics Open*, 7: 525-536.
- Breyer, F., Zweifel, P., Kifmann, M. (2009). *Health Economics*. Second Edition, Heidelberg: Springer.
- Brouwer W. (2019). The inclusion of spillover effects in economic evaluations: not an optional extra. *PharmacoEconomics*, 37 (4): 451-456.
- Brouwer W. (2023). The Value of Health in a Cost-Effectiveness Analysis: Theory Versus Practice. *PharmacoEconomics*, 41 (6): 607–617.
- Brouwer, W., van Baal, P. (2023). Moving forward with taking a societal perspective: a themed issue on productivity

costs, consumption costs and informal care costs. *PharmacoEconomics*, 41 (9): 1027-1030.

- Brouwer, W., van Exel, J., Baker, R., Donaldson, C. (2008a). *The New Myth: The Social Value of the QALY. (Editorial.)* Pharmacoeconomics 26 (1): 1-4.
- Brouwer, W.B.F., Culyer, A.J., van Exel, N.J.A., Rutten, F.F.H. (2008b). Welfarism vs. extra-welfarism. *Journal of Health Economics*, 27: 325-338.
- Brown, M.M., Brown, G.C., Sharma, S. (2005). *Evidence-Based to Value-Based-Medicine*. Chicago, IL: American Medical Association (AMA) Press.
- Buchanan, J., Wordsworth, S. (2015). Welfarism versus extra-welfarism: can the choice of economic evaluation approach impact on the adoption decisions recommended by economic evaluation studies? *PharmacoEconomics*, 33 (6): 571-579.
- Burrell, I. (1997). Thank God … it's a miracle. *The Independent*. https://www.independent.co.uk/news/thank-god-its-a-miracle-1282403.html; last accessed December 29, 2025.
- CADTH (2017). *Guidelines for the economic evaluation of health technologies: Canada. 4th ed.* Ottawa: Canadian Agency for Drugs and Technologies in Health. https://www.cda-amc.ca; last accessed May 10, 2025.
- Calabresi, G., Bobbitt, P. (1978). *Tragic Choices*. New York, NY, London: Norton & Company.
- Callahan D. (1987). *Setting Limits: Medical Goals in an Aging Society.* New York: Simon & Schuster.
- Calvert, M., Kyte, D. Price, G., Valderas, J.M., Hjollund, N.H. (2019). Maximising the impact of patient reported outcome assessment for patients and society. *British Medical Journal*, 364: k5267; doi: 10.1136/bmj.k5267.

- Caro, J.J., Brazier, J.E., Karnon, J., Kolominsky-Rabas, P., McGuire, A.J., Nord, E., Schlander, M. (2019). Determining Value in Health Technology Assessment: Stay the Course or Tack Away?. *Pharmacoeconomics*, 37 (3): 293-299.
- Carvalho, N., Vieira Sousa, T., Mizdrak, A., Jones, A., Wilson, N., Blakely, T. (2022). Comparing health gains, costs and cost-effectiveness of 100s of interventions in Australia and New Zealand: an online interactive league table. *Population Health Metrics*, 20: 17.
- Castanares T. (1991). *Statement on behalf of the Oregon Health Services Commission upon Release of the Prioritized List of Health Services, February 20, 1991*; quoted after Fox and Leichter (1991).
- Catalyst NEJM. (2017). *What is patient-centered care?. https://catalyst.nejm.org/doi/full/10.1056/CAT.17.0559*; last accessed May 05, 2026.
- CDA-AMC (2025). *Methods Guide for Health Technology Assessment – Final Report*. Canada's Drug Agency (CDA-AMC). *https://www.cda-amc.ca/methods-guide*; last accessed 09 April 2025.
- Chambers, J.D., Silver, M.C., Berklein, F.C., Cohen, J.T., Neumann, P.J. (2020). Orphan drugs offer larger health gains biz less favorable cost-effectiveness than non-orphan drugs. *Journal of General Internal Medicine*, 35 (9): 2629-2636.
- Chang L.-C. (2018). On cost effectiveness analysis and fairness: Normalizing control and resistance to NICE technology appraisals. *Financial Accounting & Management*, 37: 37-53.
- Charles River Associates (2026). *Benchmarking the UK's cost-effectiveness threshold: findings from international comparison*. Published February 04, 2026. London: Association of the British Pharmaceutical Industry (ABPI).

https://www.abpi.org.uk/publications/benchmarking-the-uk-s-cost-effectiveness-threshold-findings-from-international-comparison/; last accessed March 01, 2026.

- Charlton V. (2020). NICE and Fair? Health Technology Assessment Policy Under the UK's National Institute for Health and Care Excellence, 1999-2018. *Health Care Analysis*, *28*(3), 193–227.
- Charlton V. (2022a). Does NICE apply the rule of rescue in its approach to highly specialised technologies? *Journal of Medical Ethics*, 48: 118-125.
- Charlton V. (2022b). Justice, transparency and the Guiding Principles of the UK's National Institute for Health and Care Excellence. *Health Care Analysis*, 30: 115-145.
- Charlton V. (2024). What price is society willing to pay for new drugs? *Lancet*, 405: 3-5.
- Charlton, V., DiStefano, M. (2024). An empirical ethics study of the coherence of NICE technology appraisal policy and its implications for moral justification. *BMS Medical Ethics*, 25: 28.
- Charlton, V., Littlejohns, P., Kieslich, K., Michell, P., Rumbold, B., Weale, A., Wilson, J., Rid, A. (2017). Cost effective but unaffordable: an emerging challenge for health systems. *British Medical Journal*, 356: j1402.
- Charlton, V., Lomas, J., Mitchell, P. (2022). NICE's new methods: putting innovation first, but at what cost? *British Medical Journal*, 379: e711974. Doi: 10.1136/bmj-2022-0711974.
- Charlton, V., DiStefano, M., Mitchell, P., Morrell, L., Rand, L., Badano, G., Baker, R., Calnan, M., Chalkidou, K., Culyer, A., Howdon, D., Hughes, D., Lomas, J., Max, C., McCabe, C., O'Mahony, J.F., Paulden, M., Pemberton-Whiteley, Z., Rid, A., Scuffham, P., Sculpher, M., Shah, K., Weale, A., Wester, G. (2024). We need to talk about values: a proposed

framework for the articulation of normative reasoning in health technology assessment. *Health Economics, Policy and Law*, 19: 153-173.

- Chidgey, J., Leng, G., Lacey, T. (2007). Implementing NICE guidance. *Journal of the Royal Society of Medicine*, 100: 448-452.
- Chowdhury, S. R., Chandra Das, D., Sunna, T. C., Beyene, J., Hossain, A. (2023). Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis. *EClinicalMedicine*, 57: 101860.
- Chu, M.M., Garcia, J.T., Sedaghat, A.R., Scangas, G.A., Phillips, K.M. (2025). A cost utility analysis for the management of acute exacerbations of chronic rhinosinusitis. *International Forum of Allergology & Rhinology*, 15 (2): 109-119.
- Claxton, K., Martin, S., Soares, M., Rice, N., Spackman, E., Hinde, S., Devlin, N., Smith, P.R., Sculpher, M. (2013). *Methods for the Estimation of the NICE Cost Effectiveness Threshold. Final Report. CHE Research Paper 81*. York: Centre for Health Economics, University of York.
- Claxton, K., Martin, S., Soares, M., Rice, N., Spackman, E., Hinde, S., Devlin, N., Smith, P.R., Sculpher, M. (2015). Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technology Assessment*, 19 (14): 1–503, v–vi.
- Cleemput, I., Neyt, M., Thiry, N., De Laet, C., Leys, M. (2011). Using threshold values for cost per quality-adjusted life-year gained in healthcare decisions. *Int J Technol Assess Health Care*, 27 (1): 71-76.
- Clifford, K.A., Levine, A.A., Enright, D.E., Neumann, P.J., Chambers, J.D. (2024). The health benefits, costs, and cost-

effectiveness of ultraorphan drugs. *Value in Health*, 27 (12): 1656-1661.

- Coast J. (2004). Is economic evaluation in touch with society's health values? *British Medical Journal*, 239 (7476): 1233-1236.
- Coast J (2009). Maximisation in extra-welfarism: A critique of the current position in health economics. *Soc Sci Med*, 69 (5): 786-792.
- Coast, J., Smith, R. Lorgelly, P. (2008a). Should the capability approach be applied in health economics? *Health Economics*, 17 (6): 667-670.
- Coast, J., Smith, R.D., Lorgelly, P. (2008b). Welfarism, extra-welfarism and capability: the spread of ideas in health economics. *Social Science & Medicine*, 67 (7): 1190-1198.
- Coast, J., Bailey, C., Canaway, A., Kinghorn, P. (2021). "It is not a scientific number it is just a feeling": Populating a multi-dimensional end-of-life decision framework using deliberative methods. *Health Economics*, 30: 1033–1049.
- Cohen, I.G., Daniels, N., Eyal, N. (eds.). (2015). *Identified versus Statistical Lives. An Interdisciplinary Perspective*. New York, N.Y.: Oxford University Press.
- Collins, S.R., Roy, A., Masitha, R. (2023). *Paying for It: How Health Care Costs and Medical Debt Are Making Americans Sicker and Poorer: Findings from the Commonwealth Fund 2023 Health Care Affordability Survey*. Commonwealth Fund. October 2023. https://doi.org/10.26099/bf08-373; last accessed December 10, 2025.
- Conwell, L.J., Cohen, J.W. (2005). *Characteristics of Persons with High Medical Expenditures in the U.S.* Civilian Noninstitutionalized Population, 2002. Statistical Brief 73. Rockville: Agency for Healthcare Research and Quality.

https://meps.ahrq.gov/mepsweb/data_files/publications/st73/stat73.pdf; last accessed 20 Apr 2026.

- Cookson R. (2013). Can the NICE end-of-life premium be given a coherent ethical justification? *Journal of Health Politics, Policy and Law*, 38: 1129-1148.
- Cookson, R., McCabe, C., Tsuchiya, A. (2008). Public healthcare resource allocation and the rule of rescue. *Journal of Medical E*thics, 34: 323-329.
- Cookson, G., Garau, M., Sampson, C. (2026). *NICE's new cost-effectiveness threshold: significance, consequences, and unanswered questions*. London: Office of Health Economics (OHE). https://www.ohe.org/insights/nices-new-cost-effectiveness-threshold-significance-consequences-and-unanswered-questions/; last accessed March 04, 2026.
- Cortaredona, S., Ventelou, B. (2017). The extra cost of comorbidity: multiple illnesses and the economic burden of non-communicable diseases. *BMC Medicine*, 15(1): 216.
- Coulter, A., Oldham, J. (2016). Person-centred care: what is it and how do we get there?. *Future Hospital Journal*, 3(2): 114-116.
- Cowling, T., Nayakarathna, R., Wills, A.L., Tankala, D., Roc, N.P., Barakat, S. (2023). Early access for innovative oncology medicines: a different story in each nation. *Journal of Medical Economics*, 26: 944-953.
- Culyer A.J. (1971a). Merit goods and the welfare economics of coercion. *Public Finance*, 26: 546-572.
- Culyer A.J. (1971b). The nature of the commodity "health care" and its efficient allocation. *Oxford Economic Papers*, 23: 189-211.
- Culyer A.J. (1992). The morality of efficiency in health care - some uncomfortable implications. *Health Economics*, 1 (1): 7-18.

- Culyer A.J. (1997). The rationing debate: maximising the health of the whole community - the case for. *British Medical Journal*, 314: 667-669.
- Culyer A.J. (2006). NICE's use of cost effectiveness as an exemplar of a deliberative process. *Health Economics, Policy, and Law*, *1* (3), 299–318.
- Culyer A.J. (2016). Cost-effectiveness thresholds in health care: a bookshelf guide to their meaning and use. *Health Economics, Policy and Law*, 11 (4): 415-432.
- Culyer, A.J., Newhouse, J.P. (2000). *Handbook of Health Economics*. Amsterdam: North Holland / Elsevier.
- Dakin, H.A., Devlin, N.J., Odeyemi, I.A.O. (2006). "Yes", "no" or "yes, but"? Multinomial modelling of NICE decision-making. *Health Policy*, 77: 352-367.
- Dakin, H., Devlin, N., Feng, Y., Rice, N., O'Neill, P., Parkin, D. (2015). The Influence of Cost-Effectiveness and Other Factors on Nice Decisions. *Health Economics*, *24* (10), 1256–1271.
- Daniels N. (1979). Wide reflective equilibrium and theory acceptance in ethics. *Journal of Medical Philosophy*, 76: 256–282.
- Daniels N. (1993). Rationing fairly: programmatic considerations. *Bioethics*, 7 (2): 225-233.
- Daniels N. (2000). Accountability for reasonableness. Establishing a fair process for priority setting is easier than agreeing on principles. *British Medical Journal*, 321 (7272): 1300-1301.
- Daniels N. (2001). Justice, health, and healthcare. *American Journal of Bioethics* 2001; 1 (2): 2-16.
- Daniels N. (2008). *Just Health. Meeting Health Needs Fairly*. Cambridge, UK: Cambridge University Press.

- Daniels N. (2012). Reasonable disagreement about identified vs. statistical victims. *Hastings Center Report*, 42 (1): 35-45.
- Daniels N. (2015). Can there be moral force to favoring an identified over a statistical life? In: Cohen, I.G., Daniels, N., Eyal, N. (eds.). (2015). *Identified versus Statistical Lives. An Interdisciplinary Perspective*. New York, N.Y.: Oxford University Press, pp. 110-123.
- Daniels, N., Sabin, J. (1997). Limits to health care: fair procedures, democratic deliberation, and the legitimacy problem for insurers. *Philosophy and Public Affairs*, 26 (4): 303-350.
- Daniels, N., Sabin, J.E. (1998). The ethics of accountability in managed care reform. *Health Affairs*, 17: 50-64.
- Daniels, N., Sabin, J.E. (2002). *Setting limits fairly – can we learn to share medical resources?* Oxford: Oxford University Press.
- Danko, D., Blay, J.Y., Garrison, L.P. (2019). Challenges in the value assessment, pricing and funding of targeted combination therapies in oncology. *Health Policy*, 123 (12): 1230–1236.
- Dawson, A., Verweij, M. (2012). Solidarity: a moral concept in need of clarification. *Public Health Ethics*, 5 (1): 1-5.
- Department of Health. (2015). *The NHS constitution for England*. London: Department of Health, 2015. *www.gov.uk/government/uploads/system/uploads/attachment_data/file/480482/NHS_Constitution_WEB.pdf*; last accessed February 15, 2025.
- Desser, A.S., Gyrd-Hansen, D., Olsen, J.A., Grepperud, S., Kristiansen, I.S. (2010). Societal views on orphan drugs: cross sectional survey of Norwegians aged 40 to 67. *British Medical Journal*, 341: c4715, 1–6.

- Detiček, A., Locatelli, I., Kos, M. (2018). Patient access to medicines for rare diseases in European countries. *Value in Health*, 21 (5): 553–560.
- Devlin, N., Parkin, D. (2004). Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. *Health Economics*, *13* (5), 437–452.
- Dintsios, C.M., Gerber, A. (2010). Response: Some essential clarifications: IQWiG comments on two critiques of the efficiency frontier approach. *Health Economics*, 19; 1139-1141.
- Dolan, P., Edlin, R. (2002). Is it really possible to build a bridge between cost-benefit analysis and cost-effectiveness analysis? *Journal of Health Economics*, 21 (5): 827-843.
- Dolan, P., Olsen, J.A. (2002). *Distributing Health Care: Economic and Ethical Issues*. Oxford, U.K.: Oxford University Press.
- Dolan, P., Shaw, R., Tsuchiya, A., Williams, A. (2005). QALY maximisation and people's preferences: a methodological review of the literature. *Health Economics* 14 (2): 197–208.
- Donaldson C. (1998). The (near) equivalence of cost-effectiveness and cost-benefit analysis. Fact or fallacy? *PharmacoEconomics*, 13 (4): 389-396.
- Donaldson, C., Baker, R., Mason, H., Jones-Lee, M., Lancsar, E., Wildman, J., Bateman, I., Loomes, G., Robinson, A., Sugden, R., Prades, J.L., Ryan, M., Shackley, P., Smith, R. (2011). The social value of a QALY: raising the bar or barring the raise?. *BMC Health Services Research*, 11: 8.
- Donaldson, C., Mugford, M., Vale, L. (eds.) (2002). *Evidence-based Health Economics – From effectiveness to efficiency in systematic review*. London: BMJ Books.

- Drummond M. (2004). Economic evaluation in health care: is it really useful or are we just kidding ourselves? *Australian Economic Review*, 37 (1): 3-11.
- Drummond, M., Towse, A. (2014). Orphan drugs policies: a suitable case for treatment. *European Journal of Health Economics*, 15 (4): 335–340.
- Drummond, M.F., Stoddart, G.L., Torrance, G.W. (1987). *Methods for the Economic Evaluation of Health Care Programmes, 1st ed.* Oxford: Oxford University Press.
- Drummond, M.F., Torrance, G., Mason, J. (1993). Cost - effectiveness league tables: more harm than good? *Social Science & Medicine*, 37 (1): 33-40.
- Drummond, M.F., Wilson, D.A., Kanavos, P., Rovira, J. (2007). Assessing the economic challenges posed by orphan drugs. *International Journal of Technology Assessment in Health Care*, 23 (1): 36-42.
- Drummond, M. F., Sculpher, M. J., Claxton, K., Torrance, G. W., Stoddart, G.L. (2015). *Methods for the economic evaluation of health care programmes, 4th ed*. Oxford: Oxford University Press.
- Drummond, M., Torbica, A., Tarricone, R. (2020). Should health technology assessment be more patient centric? If so, how? *The European Journal of Health Economics*; 21 (8): 1117-1120.
- Dworkin R. (1977). *Taking Rights Seriously*. Massachusetts: Harvard University Press.
- Edejer, T.T.-T., Baltussen, R., Adam, T., Hurubessy, R., Acharya, A., Evans, D.B., Murray, C.J.L. (editors). (2003). *Making choices in health: WHO guide to cost-effectiveness analysis*. Geneva: World Health Organization.
- Edney, L.C., Haji Ali Afzali, H., Cheng, T.C., Karnon, J. (2018). Estimating the Reference Incremental Cost-

Effectiveness Ratio for the Australian Health System. *Pharmacoeconomics*, 36 (2): 239-52.

- Edney, L.C., Lomas, J., Karnon, J., Vallejo-Torres, L., Stadhouders, N., Siverskog, J., Paulden, M., Edoka, I.P., Ochalek, J. (2022). Empirical Estimates of the Marginal Cost of Health Produced by a Healthcare System: Methodological Considerations from Country-Level Estimates. *Pharmacoeconomics,* 40 (1): 31-43.
- EMA (2018). *Orphan designation: Overview*. London / Amsterdam: European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview#role-of-ema-82477; last accessed March 02, 2026.
- European Union (EU) (2021). Document 32021R2282. Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (Text with EEA relevance). *Official Journal of the European Union*, December 22, 2021, L458/1. Available online at: http://data.europa.ue/eli/reg/2021/2282/oj; last accessed July 25, 2025.
- European Union (EU) (2024). European Commission. Implementing Regulation (EU) 2024/1381 on joint clinical assessment of medicinal products for human use. https://health.ec.europa.eu/publications/implementing-regulation-eu-20241381-joint-clinical-assessment-medicinal-products-human-use_en; last accessed May 15, 2025.
- Farnsworth C. (1997). Australia rescues sailors, but is wincing at the costs. *The New York Times*. https://www.nytimes.com/1997/01/11/world/australia-rescues-sailors-but-is-wincing-at-the-costs.html; last accessed December 28, 2024.

- FDA (2025). *Focus area: Patient-Reported Outcomes and other clinical outcome assessments*. Silver Spring, MD: Food & Drug Administration (FDA), January 30, 2025. https://www.fda.gov/science-research/focus-areas-regulatory-science-report/focus-area-patient-reported-outcomes-and-other-clinical-outcome-assessments; last accessed December 20, 2025.
- Feeny, D.H., Torrance, G.W. (1989). Incorporating utility-based quality-of-life assessment measures in clinical trials. Two examples. *Medical Care*, 27 (3): Supplement, S190-S204.
- Fehr, E., Fischbacher, U. (2002). Why social preferences matter – the impact of non-selfish motives on competition, cooperation and incentives. *Economic Journal*, 112 (478): C1–C33.
- Fehr, E., Fischbacher, U. (2003). The nature of human altruism. *Nature*, 425 (6960): 785-791.
- Fernandez, J., de Boissieu, P., Galbraith, M. (2025). Health technology assessment in Europe: A comparison of organizations and introduction to the European regulation. *La Presse Médicale*, 54 (2): 104282, 1-7.
- Fitch, M.I., Sharp, L., Hanly, P., Longo, C.J. (2022). Experiencing financial toxicity associated with cancer in publicly funded healthcare systems: a systematic review of qualitative studies. *Journal of Cancer Survivorship*, 16: 314–28.
- Fleeman, N., Bagust, A., Beale, S., Dwan, K., Dickson, R., Proudlove, C., Dundar, Z. (2015). Pertuzumab in combination with trastuzumab and docetaxel for the treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer. *PharmacoEconomics*, 33 (1): 13-23.
- Fox, D.M., Leichter, H.M. (1991). Rationing care in Oregon: the new accountability. *Health Affairs (Millwood)*, 10: 7–27.

- Fried C. (1969). Value of Life. *Harvard Law Review*, 82 (7): 1415-1437.
- Friedman, B., Jiang, H.J., Elixhauser, A., Segal, A. (2006). Hospital inpatient costs for adults with multiple chronic conditions. *Med Care Res Rev.*, 63 (3): 327-346.
- Fontrier, A.M., Visintin, E., Kanavos, P. (2022). Similarities and Differences in Health Technology Assessment Systems and Implications for Coverage Decisions: Evidence from 32 Countries. *Pharmacoecon Open*, 6 (3) :315-328.
- Fuchs V.R. (1998). *Who Shall Live? Health, Economics, and Social Choice*. Singapore: World Scientific Publishing.
- Gafni, A., Birch, S. (1993). Guidelines for the adoption of new technologies: a prescription for uncontrolled growth in expenditures and how to avoid the problem. *Canadian Medical Association Journal (CMAJ)*, 148 (6): 913-917.
- Gafni, A., Birch, S. (2006). Incremental cost-effectiveness ratios (ICERS): the silence of the lambda. *Social Science & Medicine*, 62 (9): 2091-2100.
- Gammie, T., Lu, C.Y., Babar, Z.U.-D. (2015). Access to orphan drugs: a comprehensive review of legislations, regulations and policies in 35 countries. *PLOS One*, 10 (10): e0140002.
- Garau, M., Mestre-Ferrandiz, J. (2009). *Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries. OHE Briefing, No. 52, October 2009*. London: Office of Health Economics (OHE).
- Garner, S., Littlejohns, P. (2011). Disinvestment from low value clinical interventions: NICEly done? *British Medical Journal*, 343: d4519. Doi: 10.1136/bmj.d4519.
- Gemeinsamer Bundesausschuss (2025). *The benefit assessment of medicinal products in accordance with the German Social Code, Book Five (SGB V), section 35a*. Available online at:

https://www.g-ba.de/english/benefitassessment/; last accessed July 30, 2025.

- Gennet È. (2020). Introducing 'Health Vulnerability'. Towards a Human Right Claim for Innovative Orphan Drugs? *European Journal of Health Law*, 27 (3): 290-307.
- George, B., Harris, A., Mitchell, A. (2001). Cost-Effectiveness Analysis and the Consistency of Decision Making. Evidence from Pharmaceutical Reimbursement in Australia (1991 to 1996*). PharmacoEconomics*, 19 (11): 1103-1109.
- Ghabri S. (2024). Could or Should We Use Cost-Effectiveness Thresholds in the French Value-Based Pricing Process for New Drugs? *PharmacoEconomics*, 42: 823-827.
- Giacomini, M., Hurley, J., Gold, I., Smith, P., Abelson, J. (2004). The policy analysis of 'values talk': lessons from Canadian health reform. *Health Policy*, 67: 15-24.
- Glennie, J., Villalba, E., Wheatly-Price, P. (2022). Closing the Gaps to Timely Patient Access: Perspectives on Conditional Funding Models. *Current Oncology*, 29: 981-988.
- Glied, S., Smith, P. C. (2011). *The Oxford Handbook of Health Economics*. Oxford: Oxford University Press.
- Gold, M. R., Siegel, I. E., Russell, L. B., & Weinstein, M. E. (1996). *Cost-effectiveness in health and medicine*. New York: Oxford University Press.
- Gonçalves E. (2022). Value-based pricing for advanced therapy medicinal products: emerging affordability solutions. *Eur J Health Econ.*, 23 (2): 155-163.
- Goranitis, I., Coast, J., Day, E., Copello, A., Freemantle, N., Frew, E. (2017). Maximizing health or sufficient capability in economic evaluation? A methodological experiment of treatment for drug addiction. *Medical Decision Making*, 37 (5): 498-511.

¬ Greenhalgh, T., Peacock, R. (2005). Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. *BMJ (Clinical research ed.)*, *331* (7524): 1064–1065.

¬ Griffiths, E.A., Vadlamudi, N.K. (2016). CADTH's 50,000 Cost-Effectiveness Threshold: Fact or Fiction? *Value in Health*, 19: A488.

¬ Grover, S., Fitzpatrick, A., Tabassum Azim, F., Ariza-Vega, P., Bellwood, P., Burns, J., Burton, E., Fleig, L., Clemson, L., Hoppmann, C.A., Madden, K.M., Price, M., Langford, D., Ashe, M.C. (2022). Defining and implementing patient-centered care: An umbrella review. *Patient Education and Counseling*, 105 (7): 1679-1688.

¬ Gu, Y., Lancsar, E., Ghijben, P., Butler, R.G., Donaldson, C. (2015). Attributes and weights in health care priority setting: a systematic review of what counts and to what extent. *Social Science & Medicine*, 146: 41–52.

¬ Gupta, S., Syrimi, Z., Hughes, D.M., Zhao, S.S. (2021). Comorbidities in psoriatic arthritis: a systematic review and meta-analysis. *Rheumatology International*, 41 (2): 275-284.

¬ Gyrd-Hansen D. (2005). Willingness to pay for a QALY: theoretical and methodological issues. *PharmacoEconomics*, 23 (5): 423-432.

¬ Hale, G., Morris, Barker-Yip, J. (2023). Flexibility in assessment of rare disease technologies via NICE's single technology appraisal route: a hematic analysis. *Journal of Comparative Effectiveness Research*, 12 (11): e230093.

¬ Hanchard M.S. (2025). Debates over orphan drug pricing: a meta-narrative literature review. *Orphanet Journal of Rare Diseases*, 20: 107.

¬ Harris J. (1987). QALYfying the value of life? *Journal of Medical Ethics*, 13: 117-123.

- Harris J. (2005a). It's not NICE to discriminate. *Journal of Medical Ethics*, 31 (7): 373-375.
- Harris J. (2005b). Nice and not so nice. *Journal of Medical Ethics*, 31 (12): 685-688.
- Harris, R.A., Nease, R.F. (1997). The importance of patient preferences for comorbidities in cost-effectiveness analyses. *Journal of Health Economics*, 26 (1): 113-119.
- Harris, A.H., Hill, SA.R., Chin, G., Li, J.J., Walkom, E. (2008). The Role of Value for Money in Public Insurance Coverage Decisions for Drugs in Australia: A Retrospective Analysis 1994-2004. *Medical Decision Making*, 28: 713-728.
- Henshall, C.H., Dankó, D., Barham, L., Espín, J., Felix, J., Harney, M., Indra, P., Mestre-Ferrandiz, J., de Pouvourville, G., Spandonaro, F., Vončina, L., Wilking, N. (2023). Review and assessment of policy options for improving access to combination therapies in oncology in Europe. *Applied Health Economics and Health Policy*, 21 (4): 537-546.
- Hernandez, D., Schlander, M. (2021). Income loss after a cancer diagnosis in Germany: An analysis based on the socio-economic panel survey. *Cancer Medicine*, 10: 3726-3740.
- Hernandez-Viver, A., Mitchell, E.M. (2024). *Concentration of Healthcare Expenditures and Selected Characteristics of Persons with High Expenses, United States Civilian Noninstitutionalized Population, 2021*. Statistical Brief #556. March 2024. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ).
- Hernandez-Viver, A., Mitchell, E.M. (2025). *Concentration of Healthcare Expenditures and Selected Characteristics of Persons with High Expenses, United States Civilian Noninstitutionalized Population, 2018-2022*. Statistical Brief #560. March 2025. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ).

- Hirth, R.A., Chernew, M.E., Miller, E., Fendrick, M.A., Weissert, W.G. (2000). Willingness to Pay for a Quality-adjusted Life Year: In Search of a Standard. *Medical Decision Making*, 20: 332-342.
- Ho, I. S., Azcoaga-Lorenzo, A., Akbari, A., Davies, J., Hodgins, P., Khunti, K., Kadam, U., Lyons, R., McCowan, C., Mercer, S. W., Nirantharakumar, K., Guthrie, B. (2022). Variation in the estimated prevalence of multimorbidity: systematic review and meta-analysis of 193 international studies. *BMJ Open*, 12(4), e057017.
- Holle, M., Wolff, T., Herant, M. (2021). Trends in the concentration and distribution of health care expüenditures in the US, 2001-2018. *JAMA Network Open*, 4 (90): e2125179.
- Holm, S., Schlander, M. (2025). Population health impact of NICE-recommended new drugs. *The Lancet*, 405 (10497): 2276.
- Hopia, H., Latvala, E., Liimatainen, L. (2016). Reviewing the methodology of an integrative review. *Scandinavian Journal of Caring Sciences*, *30* (4): 662–669.
- Hsu J. (2023). Incorporating real-world data in cost-effectiveness analysis: challenges and opportunities. *PharmacoEconomics Open*, 8 (3), 173.
- Hughes D.A. (2015). NICE recommendations: why no disinvestment recommendations to offset investment decisions? *British Medical Journal*, 350: h2656. https://doi.org/10.1136/bmj.h265.
- Hughes, D.A., Ferner, R.E. (2010). New drugs for old – disinvestment and NICE. *British Medical Journal*, 340: c572. doi: 10.1136/bmj.c572.
- Hughes-Wilson, W., Palma, A., Schuurman, A., Simoens, S (2012). Paying for the orphan drug system: break or bend? Is it time for a new evaluation system for payers in Europe to

take account of new rare disease treatments? *Orphanet Journal of Rare Diseases*, 7 (74): 1–8.

- Husted, J.A., Thavaneswaran, A., Chandran, V., Gladman, D.D. (2013). Incremental effects of comorbidity on quality of life in patients with psoriatic arthritis. *Journal of Rheumatology*, 40 (8): 1349-1356.
- Hyle, E.P., Scott, J.A., Sax, P.E., Millham, L.R.I., Dugdale, C.M., Weinstein, M.C., Freedberg, K.A., Walensky, R.P. (2020). Clinical impact and cost-effectiveness of genotype testing at human immunodeficiency virus diagnosis in the United States. *Clinical Infectious Diseases*, 70 (7): 1353-1363.
- Hyry, H.I., Roos, J.C.P., Manuel, J., Cox, T.M. (2013). The legal imperative for treating rare disorders. *Orphanet Journal of Rare Diseases*, 8: 135: 1-7.
- IQWiG (2009). *General Methods for the Assessment of the Relation of Benefits to Costs. Version 1.0.* Cologne: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, November 19, 2009. Available online at: *https://www.iqwig.de/methoden/general_methods_for_the_assessment_of_the_rela.pdf*; last accessed January 25, 2025.
- IQWiG (2023). *IQWiG General Methods Version 7.0 (19 September 2023).* Cologne: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. *https://www.iqwig.de*; last accessed 20 January 2025.
- IQWiG (2025). *Allgemeine Methoden. Entwurf für Version 8.0 vom 25.02.2025*. Cologne: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Available online: *https://www.iqwig.de/methoden/allgemeine-methoden_entwurf-fuer-version-8-0.pdf*; last accessed July 25, 2025.
- Inhestern, L., Johannsen, L.M., Bergelt, C. (2021). Families affected by parental cancer: quality of life, impact on

children and psychosocial care needs. *Frontiers in Psychiatry*, 12: 765327.

- Isaacs D. (2014). Ethical dilemmas about orphan drugs for orphan diseases. *Journal of Paediatrics and Child Health*, 50 (4): 249-250.
- Iyengar, S., Tay-Teo, K., Vogler, S., Beyer, P., Wiktor, S., de Joncheere, K., Hill, S. (2016). Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis. *PLoS Medicine*, 13 (5): e1002032.
- Jackson D. (2012). *Healthcare Economics Made Easy*. Banbury, Oxfordshire: Scion Publishing.
- Jacobs, L., Marmor, T., Oberlander, J. (1999). The Oregon Health Plan and the political paradox of rationing: what advocates and critics have claimed and what Oregon did. *Journal of Health Politics, Policy and Law,* 24, 161-180.
- Jayasundara, K., Hollis, A., Krahn, M., Mamdani, M., Hoch, J.S., Grootendorst, P. (2019). Estimating the clinical cost of drug development for orphan versus non-orphan drugs. *Orphanet Journal of Rare Diseases*, 14 (1): 12.
- Jenei, K., Raymakers, A.J.N., Bayle, A., Berger-Thürmel, K., Cherla, A., Honda, K., Jackson, C.C.G.A., Karikios, D., Trapani, D., Berry, S., Gyawali, B. (2023). Health technology assessment for cancer medicines across the G7 countries and Oceania: an international, cross-sectional study. *Lancet Oncology*, 24 (6): 624-635.
- Jiang, H., Lyu, J., Mou, W., Jiang, Q., Du, J. (2023). Association between financial toxicity and health-related quality of life in cancer survivors: a systematic review. *Asia Pacific Journal of Clinical Oncology*, 19: 439–57.
- Johannesson, M., O'Conor, R.M. (1997). Cost-utility analysis from a societal perspective. *Health Policy*, 39 (3), 241-253.

- Johannesson, M., Weinstein, M.C. (1993). On the decision rules of cost-effectiveness analysis. *J Health Econ*, 12 (4) :459-67.
- Jonsen A. (1986). Bentham in a box: Technology assessment and health care allocation. *Law in Medicine and Health Care*, 14: 172-174.
- Juth N. (2017). For the Sake of Justice: Should We Prioritize Rare Diseases? *Health Care Analysis*, 25 (1): 1-20.
- Juth, N., Henriksson, M., Gustavsson, E., Sandman, L. (2021). Should we accept a higher cost per health improvement for orphan drugs? A review and analysis of egalitarian arguments. *Bioethics*, 35 (4): 307-314.
- Kamal-Yanni M. (2015). Hepatitis C drug affordability. *Lancet Global Health*, 3 (2): E73-E74.
- Kaplan R.M. (2009). *Disease, diagnoses, and dollars. Facing the ever-expanding market for medical care*. New York, NY: Copernicus Books.
- Kaplan, R.M., Neumann, P.J., Salomon, J.A., Gold, M.R. (2024). House QALY ban could harm, not help, people with disabilities and chronic illness. *Health Affairs Forefront*, May 3, 2024. *https://www.healthaffairs.org/content/forefront/house-qaly-ban-could-harm-not-help-people-disabilities-and-chronic-illness*; last accessed December 21, 2025.
- Karikios, D.J., Chim, L., Martin, A., Nagrial, A., Howard, K., Salkeld, G., Stockler, M.R. (2017). Is it all about price? Why requests for government subsidy of anticancer drugs were rejected in Australia. *Internal Medicine Journal*, 47: 400–407.
- Khor, S., Elsisi, Z.A., Carlson, J.J. (2023). How Much Does the US Public Value Equity in Health? A Systematic Review. *Value in Health,* 26 (3): 418-426.
- Kinghorn, P., Coast, J. (2019). Appropriate frameworks for economic evaluation of end of life care: a qualitative

investigation with stakeholders. *Palliative Medicine*, 33 (7): 823-831.

- Kinney J. (2014). Health disparities: exploring the ethics of orphan drugs. *American Journal of Health-System Pharmacy*, 71 (9): 692-693.
- Kitano, T., Yoshida, S. (2025). Impact of inactivated influenza vaccination on health-related quality of life among Japanese healthcare workers. *Immunity, Inflammation and Disease*, 13 (9): e70266.
- Kitzhaber J. (2024). *How Oregon got the 1115 waiver from the Clinton administration to implement the Oregon Health Plan*. https://blog.johnkitzhaber.com/how-oregon-got-the-1115-waiver-from-the-clinton-administration-to-implement-the-oregon-health-plan/; last accessed March 26, 2026.
- Klonschinski A. (2016). *The Economics of Resource Allocation in Health Care. Cost-utility, social value, and fairness*. Abingdon, Oxon., New York, N.Y.: Routledge.
- Knight C. (2025). *Reflective Equilibrium", The Stanford Encyclopedia of Philosophy* (Spring 2025 Edition). Zalta, E.N, Nodelman, U. (eds.). https://plato.stanford.edu/archives/spr2025/entries/reflective-equilibrium; last accessed December 15, 2025.
- Kobelt G. (2013). *Health Economics: An Introduction to Economic Evaluation*. Monograph. London: Office of Health Economics. https://www.ohe.org/publications/health-economics-introduction-economic-evaluation/; last accessed January 17, 2026.
- Korchagina, D., Jaroslawski, S., Jadot, G. Toumi, M. (2019). Orphan drugs in oncology. *Recent Results in Cancer Research*, 213: 109-142.
- Krikorian, A., Maldonado, C., Pastrana, T. (2020). Patient's perspectives on the notion of a good death: a systematic

review of the literature. *Journal of Pain and Symptom Management*, 59 (1): 152-164.

- Kumar, G., Radu, P., Cubi-Molla, P., Garau, M., Bell, E., Pan, J., Gilardino, R., Van Bavel, J., Brandtmüller, A., Nelson, K., Goodall, M. (2025). Navigating Change: A Comparative Analysis of Health Technology Assessment Reforms Across Agencies - Processes, Drivers, and Interdependencies. *International Journal of Technology Assessment in Health Care*, 1–30. [Advance online publication.]
- Kurzban, R., Burton/Chellew, M.N., West, S.A. (2015). The evolution of altruism in humans. *Annual Review of Psychology*, 66: 575-599.
- Láinez M.J. (2009). The effect of migraine prophylaxis on migraine-related resource use and productivity. *CNS Drugs*, 23 (9): 727-738.
- Lakdawalla, D.N., Doshi, J.A., Garrison, L.P., Phelps, C.E., Basu, A., Danzon, P.M. (2018). Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report. *Value in Health*, 21 (2): 131-139.
- Lancsar, E., Gu, Y., Gyrd-Hansen, D., Butler, J., Ratcliffe, J., Bulfone, L., Donaldson, C. (2020). The relative value of different QALY types. *Journal of Health Economics*, 70: 102303.
- Latimer, N. R., Towse, A., Henshall, C. (2021). Not cost-effective at zero price: valuing and paying for combination therapies in cancer. *Expert Review in Pharmacoeconomics and Outcomes Research*, 21: 331–333.
- Lavelle, T.A., Kent, D., Lundquist, C., Thorat, T., Cohen, J.T., Wog, J.B., Olchanski, N., Neumann, P.J. (2018). Patient variability seldom assessed in cost-effectiveness studies. *Medical Decision Making*, 38 (4): 487-494.
- Lee, D., McCarthy, G., Saeed, O., Allen, R., Malottki, K., Chandler, F. (2023). The challenge for orphan drugs remains:

three case studies demonstrating the impact of changes to NICE methods and processes and alternative mechanisms to value orphan products. *PharmacoEconomics Open*, 7: 175-187.

- Lewison, G. Aggarwal, A., Rose, P., Moller, H., Chamberlain, C., Sullivan, R. (2018). UK newspaper reporting of the NHS cancer drugs fund, 2010 to 2015: a retrospective media analysis. *Journal of the Royal Society of Medicine*, 111 (10): 366-373.
- Linley, W.G., Hughes, D.A. (2013). Societal views on NICE, cancer drugs fund and value-based pricing criteria for prioritizing medicines: a cross-sectional survey of 4118 adults in Great Britain. *Health Economics*, 22: 948–964.
- Lloyd-Williams H, Hughes DA. (2021). A systematic review of economic evaluations of advanced therapy medicinal products. *Br J Clin Pharmacol.,* 87 (6): 2428-2443.
- Löblová O. (2016). Three worlds of health technology assessment explaining patterns of diffusion of HTA agencies in Europe. *Health Economics, Policy and Law*, 11 (3): 253-273.
- Lomas, J., Martin, S., Claxton, K. (2019). Estimating the marginal productivity of the English National Health Service from 2003 to 2012. *Value Health*, 22: 995-1002.
- Lomas, J., Claxton, K., Ochalek, J. (2022a). Accounting for country- and time-specific values in the economic evaluation of health-related projects relevant to low- and middle-income countries. *Health Policy and Planning*, 37 (1): 45-54.
- Lomas, J., Ochalek, J., Faria, R. (2022b). Avoiding Opportunity Cost Neglect in Cost-Effectiveness Analysis for Health Technology Assessment. *Applied Health Economics and Health Policy*, 20 (1): 13-18.
- Longo C.J. (2023). Societal perspectives and real-world cost-effectiveness: expanding the scope of health economics inquiry. *Current Oncology*, 30 (1): 233-235.

- Loupas, M.A., Athanasakis, K., Zavras, D. (2026). Willingness to pay per QALY: A systematic review of demand-side valuations with a focus on age and disease severity. *Applied Health Economics and Health Policy*, 24 (1): 47-63.
- Luebbe W. (2004). Lebensnotstand – Ende der Normativität? Untersuchung einer Grauzone im Unrecht des Tötens. In: Luebbe, W. (ed.) *Tödliche Entscheidung. Allokation von Leben und Tod in Zwangslagen*. Paderborn: mentis-Verlag, 104-121.
- Luebbe W. (2005). *Economizing Life and Death*. Project Syndicate, November 05, 2005. *https://www2.project-syndicate.org/commentary/economizing-life-and-death-2005-11*; last accessed November 05, 2025.
- Luebbe W. (2015). *Nonaggregationismus. Grundlagen der Allokationsethik*. Münster: mentis.
- Luebbe W. (2017). Rule of Rescue versus Rettung statistischer Leben. *Das Gesundheitswesen*, 79 (10): 877-882.
- Luzzatto, L., Hyry, H.I., Schieppati, A., Costa, E., Simoens, S., Schaefer, F., Roos, J.C.P., Merlini, G., Kääriäinen, H., Garattini, S., Hollak, C.E., Remuzzi, G., on behalf of the Second Workshop on Orphan Drugs participants. (2018). Outrageous prices of orphan drugs: a call for collaboration. *The Lancet*, 392 (10149): 791-794.
- Lybrand, S., Wonder, M. (2020). Analysis of PBAC submissions and outcomes for medicines (2010–2018). *International Journal of Technology Assessment in Health Care*, 36 (3): 224-231.
- Makovski, T. T., Schmitz, S., Zeegers, M. P., Stranges, S., van den Akker, M. (2019). Multimorbidity and quality of life: Systematic literature review and meta-analysis. *Ageing Research Reviews*, 53, 100903.

- Marschak J. (1950). Rational behaviour, uncertain prospects, and measurable utility. *Econometrica*, 18: 11-141.
- Marseille, E., Larson, B., Kazi, D.S., Kahn, J.G., Rosen, S. (2015) Thresholds for the cost–effectiveness of interventions: alternative approaches. *Bulletin of the World Health Organization* 93 (2): 118–124.
- Martin, S., Lomas, J., Claxton, K., Longo, F. (2021). How effective is marginal healthcare expenditure? New evidence for England for 2003/04 to 2012/13. *Applied Health Economics and Health Policy*, 19 (6): 885-903.
- Marupuru, S., Axon, D.R. (2021). Association of Multimorbidity on Healthcare Expenditures Among Older United States Adults With Pain. *Journal of Aging and Health*, 33 (9): 741-750.
- Mason, J., Drummond, M., Torrance, G. (1993). Some guidelines on the use of cost effectiveness league tables- *British Medical Journal*, 306: 570-572.
- Mauskopf, J., Rutten, F., Schonfeld, W. (2003). Cost–effectiveness league tables: valuable guidance for decision makers? *PharmacoEconomics*, 21(14): 991–1000.
- Mauskopf, J., Chirila, C., Masaquel, C., Boye, K.S., Bowman, L., Birt, J., Grainger, D. (2013). Relationship between financial impact and coverage of drugs in Australia. *International Journal of Technology Assessment in Health Care*, 29: 92–100.
- McCabe, C., Claxton., K., Tsuchyia, A. (2005). Orphan drugs and the NHS: should we value rarity? *British Medical Journal*, 331 (7523): 1016-1019. Doi: 10.1136/bmj.331.7523.1016.
- McCabe, C., Claxton, K., Culyer, A.J. (2008). The NICE cost-effectiveness threshold: what it is and what that means. *PharmacoEconomics*, *26*(9): 733–744.

- McCulloch D. (2003). *Valuing Health in Practice: Priorities, QALYs, and Choice.* Burlington, VT: Ashgate Publishing.
- McDaid, D., Park, A.-L. (2014). Counting all the costs: the economic impact of comorbidity. In: Sartorius, N., Holt, R.I.G., Maj, M. (eds.). *Comorbidity of mental and physical disorders*. Basle, Switzerland: S. Karger, pp. 23-32.
- McKie, J., Richardson, J. (2003). The rule of rescue. *Social Science & Medicine*, 56: 2407-2419.
- McPhail S.M. (2016). Multimorbidity in chronic disease: impact on health care resources and costs. *Risk Management and Healthcare Policy*, 9: 143–156.
- McQueen, R.B., Wailoo, A., Tsuchyia, A., Cipriano, L.E., Geurtin, J.R., Sanders Schmidler, G.D., Steuten, L., Sullivan, S., Thavorn, K., Sculpher, M. (2026). *Defining Appropriate Benefits for Economic Evaluation of Health Care Technologies.* Health Economics Methods Advisory Group. *https://hemamethods.org/wp-content/uploads/2026/03/HEMA-Report_For-Publication_031126.pdf*; last accessed March 26, 2026.
- Meropol S.B. (2008). Valuing reduced antibiotic use for pediatric acute otitis media. *Pediatrics*, 121 (4): 669-673.
- Mitchell, P.M., Venkatapuram, S., Richardson, J., Iezzi, A., Coast, J. (2017). Are quality-adjusted life years a good proxy measure of individual capabilities? *PharmacoEconomics*, 35: 637-646.
- Mooney G. (2009). *Challenging Health Economics*. Oxford, UK: Oxford University Press.
- Mooney, H., Kesselheim, A.S., Rome, B.N. (2025). US spending on high-revenue rare disease drugs in 2022. *American Journal of Managed Care*, 31 (11): e329-e335.
- Moro, D. Schlander, M., Telser, H., Sola-Morales, O., Clark, M.D., Olaye, A., Camp, C., Jain, M., Butt, T., Bakshi, S.

(2022). Evaluating discrete choice experiment willingness to pay [DCE-WTP] analysis and relative social willingness to pay [RS-WTP] analysis in a health technology assessment of a treatment for an ultra-rare childhood disease [CLN2]. *Expert Review of Pharmacoeconomics & Outcomes Research*, 22 (4): 581-598.

- Morrell, L., Wordsworth, S., Schuh, A., Middleton, M.R., Rees, S., Barker, R.W. (2018). Will the reformed Cancer Drugs Fund address the most common types of uncertainty? An analysis of NUICE cancer drug appraisals. *BMC Health Services Research*, 18: 393.
- Mrozek, J.R., Taylor, L.O. (2002) What determines the value of life? A meta-analysis. *Journal of Policy Analysis and Management*, 21 (2):253–270.
- Muennig P., Bounthavong, M. (2016). *Cost-Effectiveness Analysis in Health: A Practical Approach*. San Francisco: Jossey-Bass, Wiley (3rd ed.).
- Mueller, M., Huembelin, M., Baechli, C., Wagner, U., Schuetz, P., Mueller, B., Kutz, A. (2021). Association of in-hospital multimorbidity with healthcare outcomes in Swiss medical inpatients. *Swiss Medical Weekly*, 151: w20405. Doi: 10.4414/smw.2021.20405.
- Murphy, P., Griffin, S., Walker, S., Vallejo-Torres, L., Espinosa, O., Gloria, M.A.J., Ochalek, J. (2026). Cost-effectiveness thresholds in policy and practice: do HTA guidelines align with estimates of health opportunity cost? *Health Economics, Policy and Law*, 1-29. https://doi.org/10.1017/S1744133126100395; last accessed March 28, 2026.
- Naci, J.H., Murphy, P., Woods, B., Lomas, J., Wei, J., Papanicolas, I. (2025). Population-health impact of new drugs recommended by the National Institute for Health

and Care Excellence in England during 2000-20: a retrospective analysis. *The Lancet*, 405 (10472): 50-60.

- Neumann P.J. (2005). *Using cost-effectiveness analysis to improve health care: opportunities and barriers*. Oxford and New York, NY: Oxford University Press.
- Neumann, P.J., Weinstein, M.C. (2010). Legislating against use of cost-effectiveness information. *New England Journal of Medicine*, 363 (16): 1495-1497
- Neumann, P.J., Cohen, J.T., Weinstein, M.C. (2014). Updating cost-effectiveness – the curious resilience of the $50,000-per-QALY threshold. *New England Journal of Medicine*, 371 (9): 796-797.
- Nguyen, H., Manolova, G., Daskalopoulou, C., Vitoratou, S., Prince, M., Prina, A.M. (2019). Prevalence of multimorbidity in community settings: A systematic review and meta-analysis of observational studies. *J Comorb.*, 9: 2235042X19870934.
- NHS England (2016). *Cancer Drugs Fund*. London: National Health Service England. https://www.england.nhs.uk/cancer/cdf/; last accessed 09 April 2025.
- NHS England (2024). *Budget Impact Test threshold consultation*. London: National Health Service England. https://www.england.nhs.uk/long-read/budget-impact-test-threshold-consultation/; last accessed Jun 30, 2025.
- Ngo P. (2014). The Influence of Cost-Effectiveness Evaluations on Reimbursement in Australia: A Retrospective Study of Decisions made by the Pharmaceutical Benefits Advisory Committee. *Pharm Med*, 28: 187–193.
- NICE (2004a). *Guide to the Methods of Technology Appraisal*. London: National Institute for Health and Care Excellence. https://assets.publishing.service.gov.uk/media/5a7a5acee527

4a34770e6144/NICE_guide_to_the_methods_of_technology_appraisal.pdf; last accessed 10 April 2025.

- NICE (2004b). *NICE Citizens Council Report Ultra Orphan Drugs*. London: National Institute for Clinical Excellence.
- NICE (2005). *How to put NICE guidance into practice. A guide to implementation for organisations*. London: National Institute for Health and Clinical Excellence.
- NICE (2008). *Social value judgements: principles for the development of NICE guidance. 2nd edition*. London: National Institute for Health and Clinical Excellence.
- NICE (2009). *NICE Appraising life-extending, end of life treatments*. London: National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/gid-tag387/documents/appraising-life-extending-end-of-life-treatments-paper2; last accessed 08 April 2025.
- NICE (2013). *Guide to the methods of technology appraisal 2013. NICE process and methods. PMG9. Published: 04 April 2013*. London: National Institute for Health and Care Excellence. https://www.nice.org.uk/process/pmg9/chapter/the-reference-case; last accessed June 28, 2025.
- NICE (2016). *PMG19 addendum a - final amendments to the NICE technology appraisal processes and methods guides to support the proposed new Cancer Drugs Fund arrangements. 2016.* London: National Institute for Health and Care Excellence. https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/process-and-methods-guide-addendum.pdf; last accessed July 04, 2025.
- NICE (2023). *Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals. NICE process and methods. Reference number:*

PMG40. Published: 24 April 2023. London: National Institute for Health and Care Excellence. https://www.nice.org.uk/process/pmg40; last accessed March 02, 2026.

- NICE (2024a). *NICE health technology evaluations: the manual. NICE process and methods [PMG36]*. London: National Institute for Health and Care Excellence. https://www.nice.org.uk/process/pmg36; last accessed 30 January 2025.
- NICE (2024b). *A guide to the severity modifier*. London: National Institute for Health and Care Excellence. https://indepth.nice.org.uk/what-is-nices-severity-modifier/index.html; last accessed 08 April 2025.
- NICE (2025a). Changes to NICE's cost-effectiveness thresholds confirmed. London: National Institute for Health and Care Excellence, December 1, 2025. Available online at: https://www.nice.org.uk/news/articles/changes-to-nice-s-cost-effectiveness-thresholds-confirmed; last accessed December 15, 2025.
- NICE (2026). *NICE technology appraisal and highly specialised technologies guidance: the manual*. NICE process and methods. Reference number: PMG36. Published: 31 January 2022. Last updated: 31 March 2026. London: National Institute for Health and Care Excellence. https://www.nice.org.uk/process/pmg36; last accessed March 02, 2026.
- Nicod, E., Kanavos, P. (2012). Commonalities and differences in HTA outcomes: a comparative analysis of five countries and implications for coverage decisions. *Health Policy*, 108 (2-3): 167-177.
- Nilsen, P., Wassar Kirk, J., Ulfsdotter Gunnarsson, K., Thomas, K. (2025). Tempering implementation optimism:

distinguishing between efficacy and effectiveness in implementation research. *Implementation Science Communications*, 6: 90.

- Nimdet, K., Chaiyakunapruk, N., Vichansavakul, K., Ngorsuraches, S. (2015). A systematic review of studies eliciting willingness-to-pay per quality-adjusted life year: does it justify CE threshold? *PLoS One*, 10 (4): e122760. Doi: 10.1371/journal.pone.0122760.
- Niu, S., Happe, L., Abuloha, S., Svensson, M. (2024). Concentration of spending and shgare of specialty drug spending in Medicare Part D over a 10-yaer period. *Journal of Managed Care & Specialty Pharmacy*, 30 (12): 1355-1363.
- Njoroge, M.W., Walton, M., Hodgson, R. (2024). Understanding the National Institute for Health and Care Excellence Severity Premium: Exploring Its Implementation and the Implications for Decision Making and Patient Access. *Value in Health*, 27 (6): 730-736.
- Nord E. (1993). Unjustified use of the quality of well-being scale in priority setting in Oregon. *Health Policy*, 24: 45-53.
- Nord E. (1999). *Cost-Value Analysis in Health Care: Making Sense out of QALYs*. Cambridge, U.K.: Cambridge University Press.
- Nord, E., Johansen, R. (2014). Concerns for severity in priority setting in health care: a review of trade-off data in preference studies and implications for societal willingness-to-pay for a QALY. *Health Policy*, 116 (2–3): 281–288.
- Nord, E., Richardson, J., Street, A., Kuhse, H., Singer, P. (1995). Who cares about cost? Does economic analysis impose or reflect social values? *Health Policy* 34, 79–94.
- Normand C. (2012). Setting priorities in and for end-of-life care: challenges in the application of economic evaluation. *Health Economics, Policy and Law*, 7 (4): 431–439.

- Oberlander, J., Marmor, T., Jacobs, L. (2001). Rationing medical care: rhetoric and reality in the Oregon Health Plan. *Canadian Medical Association Journal (CMAJ)*, 164 (11): 1583-1587.
- Ochalek, J., Lomas, J. (2020). Reflecting the health opportunity costs of funding decisions within value frameworks: initial estimates and the need for further research. *Clinical Therapeutics*, 42 (1): 44-59.
- Ochalek, J., Lomas, J., Claxton, K. (2018a). *Assessing health opportunity costs for the Canadian health care systems.* York: University of York, Commissioned report, March 12, 2018.
- Ochalek, J., Lomas, J., Claxton, K. (2018b). Estimating health opportunity costs in low-income and middle-income countries: a novel approach and evidence from cross-country data. *BMJ Global Health*, 3 (6): e000964. Doi: 10.1136/bmjgh-2018-000964.
- Ochalek, J., Wang, H., Gu, Y., Lomas, J., Cutler, H., Jin, C. (2020). Informing a Cost-Effectiveness Threshold for Health Technology Assessment in China: A Marginal Productivity Approach. *Pharmacoeconomics*, 38 (12): 1319-1331.
- Ochalek, J., Claxton, K., Lomas, J., Thompson, K.M. (2021). Valuing health outcomes: developing better defaults based on health opportunity costs. *Expert Review of Pharmacoeconomics & Outcomes Research*, 21 (4): 729-736.
- O'Connor, A.B., Noyes, K., Holloway, R.G. (2007). A cost-effectiveness comparison of Desimipramine, gabapentin, and pregabalin for treating postherpetic neuralgia. *Journal of the American Geriatric Society*; 55 (8): 1176-1184.
- Office of Medical Assistance Programs [OMAP] (1991/1997). *The Oregon Medicaid Demonstration: Waiver Cost Estimate*. Prepared for HCFA and submitted to the Office of Medical

Assistance Programs. Salem, OR: Oregon Department of Human Resources, April 15, 1991.

- Ogden J. (2017a). Implementing NICE guidance to maximise success. *Prescriber*, May 2017: 45-48.
- Ogden J. (2017b). How will NICE's budget impact test affect new drug availability? *Prescriber*, August 2017: 9-12.
- Oh, P.I., Maerov, P., Pritchard, D., Knowles, S.R., Einarson, T.R., Shear, N.H. (1996). A cost-utility analysis of second-line antibiotics in the treatment of acute otitis media in children. *Clinical Therapeutics*, 18 (1): 160-182.
- O'Rourke, B., Oortwijn, W., Schuller, T., and the International Joint Task Group (2020). The new definition of health technology assessment: A milestone in international collaboration. *International Journal of Technology Assessment in Health Ca*re, 36: 187-190.
- Oregon Health Services Commission (1995). *Prioritization of Health Services*. *https://www.oregon.gov/oha/Pages/index.aspx*; last accessed 12 May 2026.
- Orofino, J., Soto, J., Casado, M.A., Oyagüez, I. (2010). Global spending on orphan drugs in France, Germany, the UK, Italy and Spain during 2007. *Applied Health Economics and Health Policy*, 8 (5): 301-315.
- Orr, S., Wolff, J. (2015). Reconciling cost-effectiveness with the rule of rescue: the institutional division of moral labour. *Theory and Decision*, 78 (4): 525–538.
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., McGuinness, L. A., … Moher, D. (2021). The PRISMA 2020 statement: an updated

guideline for reporting systematic reviews. *BMJ (Clinical research ed.)*, *372*: n71.

- Palladino, R., Tayu Lee, J., Ashworth, M., Triassi, M., Millett, C. (2016). Associations between multimorbidity, healthcare utilisation and health status: evidence from 16 European countries. *Age and Ageing*, 45 (3): 431–435.
- Papadopoulos, F., Visintin, E., Kyriopoulos, I., Kanavos, P. (2025). Why drugs fail health technology assessment: a comparative analysis of health technology assessment rejections across seven OECD countries. *Health Economics, Policy, and Law*, 20 (3): 264-283.
- Persson U. (2012). *Value based pricing in Sweden: lessons for design?* London: Office of Health Economics (OHE), Seminar briefing no. 12, November 2012.
- Pearson, S.D., Rawlins, M.D. (2005). Quality, innovation, and value for money. NICE and the British National Health Service. *Journal of the American Medical Association (JAMA)*, 294 (20): 2618-2622.
- Perrone, F., Jommi, C., Di Maio, M., Gimigliano, A., Gridelli, C., Pignata, S., Ciardiello, F., Nuzzo, F., de Matteis, A., Del Mastro, L., Bryce, J., Daniele, G., Morabito, A., Piccirillo, M.C., Rocco, G., Guizzaro, L., Gallo, C. (2016). The association of financial difficulties with clinical outcomes in cancer patients: secondary analysis of 16 academic prospective clinical trials conducted in Italy. *Annals of Oncology*, 27: 2224–2229.
- PHARMAC (2015). *Prescription for Pharmacoeconomic Analysis. Methods for cost-utility analysis (Version 2.2., 2015).* Wellington: Pharmaceutical Management Agency. www.pharmac.govt.nz; last accessed 24 January 2025.

- Phelps, C.E., Mushlin, A.I. (1991). On the (near) equivalence of cost-effectiveness and cost-benefit analysis. *International Journal of Technology Assessment in Health Care*, 7 (1): 12-21.
- Picavet, E., Annemans, L., Cleemput, I., Cassiman, D., Simoens, S. (2012). Market uptake of orphan drugs – a European analysis. *Journal of Clinical Pharmacy and Therapeutics*, 37 (6): 664–647.
- Pichon-Riviere, A. Drummond, M., Palacios, A., Garcia-Marti, S., Augustovski, F. (2023). Determining the efficiency path to universal health coverage: cost-effectiveness thresholds for 174 countries based on growth in life expectancy and health expenditures. *Lancet Global Health*, 11: e833-e842.
- Pichon-Riviere, A., Rodriguez-Cairoli, F., Drummond, M., Espinola, N., Gárcia-Martí, S. Augustovski, F. (2025). Affordability decision rules: a systematic review and framework for categorising budget impact thresholds across health systems. *The Lancet Global Health*, 13 (12): e2027-e2040.
- Pinheiro, V., Feldens, T., Haagsma, J.A., Santos, J.V. (2025). In varietate concordia - cluster analysis of EQ-5D-5L value sets in European Union countries. *Quality of Life Research*, 34 (4): 1091-1102.
- Pliskin, J.S., Shepard, D.S., Weinstein, M.C. (1980). Utility functions for life years and health status. *Operations Research*, 28: 206-224.
- Postma, M., Noone, D., Rozenbaum, M.H., Carter, J.A., Botteman, M.F., Fenwick, E., Garrison, L.P. (2022). Assessing the value of orphan drugs using conventional cost-effectiveness analysis: Is it fit for purpose? *Orphanet Journal of Rare Diseases*, 17: 157, 1-8.
- Radu, P., Biurrun, C., Boysen, M., Whittington, M., Skedgel, C. (2026). *The case for adopting a broader perspective on value in*

Health Technology Assessment. London: Office for Health Economics (OHE). *https://www.ohe.org/publications/the-case-for-adopting-a-broader-perspective-on-value-in-health-technology-assessment/*; last accessed March 26, 2026.

- Raftery J. (2001). NICE: faster access to modern treatments? Analysis of guidance on health technologies. *British Medical Journal*, 323: 1300-1303.
- Raftery J. (2006). Review of NICE's recommendations, 1999-2005. *British Medical Journal*, 332: 1266-1268.
- Rakowski E. (1991). *Equal Justice*. Oxford, U.K.: Oxford University Press.
- Rakowski, E. (1993). Taking and saving lives. *Columbia Law Review*, 93: 1063-1156.
- Ramsey, S.D., Bansal, A., Fedorenko, C.R., Blough, D.K., Overstreet, K.A., Shankaran, V, Newcomb, P. (2016). Financial insolvency as a risk factor for early mortality among patients with cancer. *Journal of Clinical Oncology*, 34: 980–986.
- Rand, L.Z., Kesselheim, A.S. (2021). Controversy Over Using Quality-Adjusted Life-Years In Cost-Effectiveness Analyses: A Systematic Literature Review. *Health Affairs (Millwood)*, 40 (9): 1402-1410.
- Rawles J. (1989). Castigating QALYs. *Journal of Medical Ethics*, 15: 143-147.
- Rawlins M.D. (2004). NICE and the public health. *British Journal of Clinical Pharmacology*, 58 (6): 575-580.
- Rawlins M.D. (2015). National Institute for Clinical Excellence: NICE works. *Journal of the Royal Society of Medicine*, 108: 211-219.
- Rawlins, M. D., Culyer, A. J. (2004). National Institute for Clinical Excellence and its value judgments. *British Medical Journal*, *329* (7459): 224–227.

- Rawlins, M., Dillon, A. (2005). NICE discrimination. *Journal of Medical* Ethics, 31 (12): 683-684.
- Rawls J. (1971). *A Theory of Justice*. Oxford, U.K.: Oxford University Press.
- Rawson N.S.B. (2022). Health technology assessment and price negotiation alignment for rare disorder drugs in Canada: Who benefits? *Orphanet Journal of Rare Diseases*, 17: 218.
- Rawson, N.S.B., Stewart, D.J. (2024). Timeliness of Health Technology Assessments and Price Negotiations for Oncology Drugs in Canada. *ClinicoEconomics and Outcomes Research*, 16: 437-445.
- Rejon-Parrilla, J.C., Espín, J., Garner, S., Kniazkov, S., Epstein, D. (2023). Pricing and reimbursement mechanisms for advanced therapy medicinal products in 20 countries. *Frontiers in Pharmacology*, 14: 1199500. Doi: 10.3389/fphar.2023.1199500.
- Rhee T.G. (2015). Policymaking for Orphan Drugs and Its Challenges. *AMA Journal of Ethics*, 17 (8): 776-779.
- Richardson, J., McKie, J. (2005). Empiricism, ethics and orthodox economic theory: what is the appropriate basis for decision making in the health sector? *Social Science & Medicine*, 60 (2): 265–275.
- Richardson, J., McKie, J. (2007). Economic evaluation of services for a National Health scheme: the case for a fairness-based framework. *Journal of Health Economics*, 26 (4): 785-799.
- Richardson, J., Schlander, M. (2018). Health technology assessment (HTA) and economic evaluation: efficiency or fairness first. *Journal of Market Access & Health Policy*, 7 (1): 1557981.

- Richardson, J., Sinha, K., Lezzi, A., Maxwell, A. (2012). Maximising health versus sharing: measuring preferences for the allocation of the health budget. *Social Science & Medicine*, 75: 1351–1361.
- Richardson, J., Iezzi, A., Chen, G., Maxwell, A. (2017). Communal sharing and the provision of low-volume high-cost health services: results of a survey. *PharmacoEconomics Open*, 1 (1): 13-23.
- Richardson, J., Iezzi, A., Maxwell, A. (2018). Sharing and the provision of "cost ineffective" life extending services to less severely ill patients. *Value In Health*, 21: 951-957.
- Rid, A., Littlejohns, P., Wilson, J., Rumbold, B., Kieslich, K., Weale, A. (2015). The importance of being NICE. *Journal of the Royal Society of Medicine*, 108 (10): 385–389.
- Robertson J. (2025a). NICE cost-effectiveness thresholds increased as UK strikes trade deal with United States. *The Pharmaceutical Journal*, online edition, December 02, 2025. *https://pharmaceutical-journal.com/article/news/nice-cost-effectiveness-thresholds-increased-as-uk-strikes-trade-deal-with-united-states*; last accessed December 15, 2025.
- Robertson J. (2025b). NICE medicines thresholds: what's changing and where is the money coming from? *The Pharmaceutical Journal*, online edition, December 17, 2025. *https://pharmaceutical-journal.com/article/feature/nice-medicines-thresholds-whats-changing-and-where-is-the-money-coming-from*; last accessed December 19, 2025.
- Robertson, J. (2026). MPs push for more details on VPAG and NICE threshold changes *The Pharmaceutical Journal*, online edition, December 17, 2025. *https://pharmaceutical-journal.com/article/news/mps-push-for-more-details-on-vpag-and-nice-threshold-changes;* last accessed February 20, 2026.

¬ Rodriguez-Monguio, R., Spargo, T., Seoane-Vazquez, E. (2017). Ethical imperatives of timely access to orphan drugs: is possible to reconcile economic incentives and patients' health needs? *Orphanet Journal of Rare Diseases*, 12 (1): 1.

¬ Rosenbach, M.L., Lee, A.J., Hwang, C., Garfinkel, S.A., Swigonski, N. (1997). *The Evolution of the Oregon Health Plan. First Interim Report. December 12, 1997*. Baltimore, MD: Health Care Financing Administration (HCFA).

¬ Round J. (2012). Is a QALY still a QALY at the end of life? *Journal of Health Economics*, 31 (1): 521-527.

¬ Rumbold, B., Weale, A., Rid, A., Wilson, J., Littlejohns, P. (2017). Public reasoning and healthcare priority setting: The case of NICE. *Kennedy Institute of Ethics Journal*, 27 (1): 107–134.

¬ Ruof, J., Knoerzer, D., Dunne, A.A., Dintsios, C.M., Staab, T., Schwartz, F.W. (2014a). Analysis of endpoints used in marketing authorisations versus value assessments of oncology medicines in Germany. *Health Policy*, 118 (2): 242-254.

¬ Ruof, J., Dintsios, C.M., Schwartz, F.W. (2014b). Questioning patient subgroups for benefit assessment: challenging the German Gemeinsamer Bundesausschuss approach. *Value in Health*, 17: 307-309.

¬ Russo, P., Zanuzzi, M., Carletto, A., Sammarco, A., Romano, F., Manca, A. (2023). Role of Economic Evaluations on Pricing of Medicines Reimbursed by the Italian National Health Service. *PharmacoEconomics*, 41 (1), 107–117.

¬ Ryen, L., Svensson, M. (2015). The willingness to pay for a quality-adjusted life year: a review of the empirical literature. *Health Economics*, 24 (10): 1289-1301.

¬ Salek, S., Hoskyn, S.L., Johns, J.R., Allen, N., Sehgal, C. (2019). Factors Influencing Delays in Patient Access to New

Medicines in Canada: A Retrospective Study of Reimbursement Processes in Public Drug Plans. *Frontiers in Pharmacology*, 10: 196, 1-13.

- Sampson C. (2025). There is no evidence that NICE approvals cause harm. *The Academic Health Economics Blog*, January 13, 2025. *https://aheblog.com/2025/01/13/there-is-no-evidence-that-nice-approvals-cause-harm/*; last accessed February 20, 2026.
- Sampson, C., Zamora, B., Watson, S., Cairns, J., Chalkidou, K., Cubi-Molla, P., Devlin, N., Garcia-Lorenzo, B., Hughes, D.A., Leech, A.A., Towse, A. (2022). Supply-Side Cost-Effectiveness Thresholds: Questions for Evidence-Based Policy. *Applied Health Economics and Health Policy*, 20: 651-667.
- Schaefer, R., Schlander, M. (2019). Is the National Institute for Health and Care Excellence (NICE) in England more 'innovation-friendly' than the Federal Joint Committee (G-BA) in Germany? *Expert Review of Pharmacoeconomics & Outcomes Research*, 19 (4), 453–462.
- Schaefer, R., Hernandez, D., Selberg, L., Schlander, M. (2021). Health technology assessment (HTA) in England, France and Germany: what do matched drug pairs tell us about recommendations by national HTA agencies? *Journal of Comparative Effectiveness Research*, 10 (16), 1187–1195.
- Schaefer, R., Hernández, D., Bärnighausen, T., Kolominsky-Rabas, P., Schlander, M. (2023). Health Technology Assessment–Informed Decision Making by the Federal Joint Committee / Institute for Quality and Efficiency in Health Care in Germany and the National Institute for Health and Care Excellence in England: The Role of Budget Impact. *Value in Health*, 26 (7): 1032–1044.

¬ Schelling T. (1968). The Life You Save May Be Your Own. In: Chase, S.B. (ed.). *Problems in Public Expenditure Analysis.* Washington, D.C.: The Brookings Institution, pp. 127-162.
¬ Schiltz N.K. (2022). Prevalence of multimorbidity combinations and their association with medical costs and poor health: A population-based study of U.S. adults. *Frontiers in Public Health*, 10: 953886.
¬ Schlander M. (2005a). Kosteneffektivität und Ressoucenallokation: Gibt es einen normativen Anspruch der Gesundheitsökonomie? In: Kick, H.A., Taupitz, J. (eds.) *Gesundheitswesen zwischen Wirtschaftlichkeit und Menschlichkeit*. Münster: LIT-Verlag, pp. 37-112.
¬ Schlander M. (2005b). *Economic evaluation of medical interventions: answering questions people are unwilling to ask?* Paper presented to the 5th World Congress of the International Health Economics Association (iHEA), Barcelona. Book of Abstracts, pp. 194–195.
¬ Schlander M. (2008). The use of cost-effectiveness by the National Institute for Health and Clinical Excellence (NICE): no (t yet an) exemplar of a deliberative process. *Journal of Medical Ethics*, 34: 534-539.
¬ Schlander M. (2010). Measures of efficiency in healthcare: QALMs about QALYs? *German Journal for Evidence and Quality in Health Care [Zeitschrift für Evidenz, Fortbildung und Qualität]* 104 (3), 209-226.
¬ Schlander M. (2021). HTA Agencies Need Evidence-Informed Deliberative Processes. *International Journal of Health Policy and Management*, 10 (3): 158-161.
¬ Schlander M. (2024). Health economics and resource allocation at the end of life. [German: Gesundheitsökonomie und Ressourcenallokation am Lebensende]. *Zeitschrift für medizinische Ethik*, 70: 303-326.

- Schlander, M., Beck, M. (2009). Expensive drugs for rare disorders: to treat or not to treat? The case of enzyme replacement therapy for mucopolysaccharidosis VI. *Curr Med Res Opin.*, 25 (5): 1285-1293.
- Schlander, M., Garattini, S., Holm, S., Kolominsky-Rabas, P., Nord, E., Persson, U., Postma, M., Richardson, J., Simoens, S., de Solà-Morales, O., Tolley, K., Toumi, M. (2014). Incremental cost per quality-adjusted life year gained? The need for alternative methods to evaluate medical interventions for ultra-rare disorders. *Journal of Comparative Effectiveness Research*, 3 (4): 399-422.
- Schlander, M., Garattini, S., Kolominsky-Rabas, P., Nord, E., Persson, U., Postma, M., Richardson, J., Simoens, S., de Solà-Morales, O., Tolley, K., Toumi, M. (2016). Determining the value of medical technologies to treat ultra-rare disorders: a consensus statement. *Journal of Market Access and Health Policy*, 27 (4). Doi: 10.3402/jmahp.v4.33039. eCollection 2016.
- Schlander, M., Schaefer, R., Schwarz, O. (2017). *The economic value of a statistical life year in Europe: a systematic review of European studies from 1995-2015.* Discussion Paper No. 34. Wiesbaden: InnoVal-HC.
- Schlander, M., van Harten, W., Retèl, V.P., Pham, P.D., Vancoppenolle, J.M., Ubels, J., Seoane López, O., Quirland, C., Maza, F., Aas, E., Crusius, B., Escobedo, A., Franzen, N., Fuentes-Cid, J., Hernandez, D., Hernandez-Villafuerte, K., Kirac, I., Paty, A., Philip, T., Smeland, S., Sullivan, R., Vanni, E. Varga, S., Vermeulin, T., Eckford, R.D. (2024). The socioeconomic impact of cancer on patients and their relatives: Organisation of European Cancer Institutes task force consensus recommendations on conceptual framework, taxonomy, and research directions. *Lancet Oncology*, 25 (4): e152-e163.

- Schlichting, M, Hennig, M., Rudell, K., McLeod, L., Bennett, B., Shaw, J., Doward, L., Molsen-David, E., Chassany, O. (2022). Is IQWiG's 15% threshold universally applicable in assessing the clinical relevance of patient-reported outcomes changes? An ISPOR Special Interest Group Report. *Value in Health*, 25 (9): 1463-1468.
- Schlosser, R. W., Wendt, O., Bhavnani, S., Nail-Chiwetalu, B. (2006). Use of information-seeking strategies for developing systematic reviews and engaging in evidence-based practice: the application of traditional and *comprehensive* Pearl Growing. A review. *International Journal of Language & Communication Disorders*, *41*(5): 567–582.
- Schuetz, P., Sulo, S. Walzer, S., Vollmer, L., Brunton, C., Kaegi-Braun, N., Stanga, Z., Mueller, B., Gomes, F. (2021). Cost savings associated with nutritional support in medical inpatients: an economic model based on data from a systematic review of randomised trials. *BMJ Open*, 11 (7): e046402. Doi: 10.1136/bmjopen-2020-046402.
- Schwappach D.L.B. (2002). Resource allocation, social values and the QALY: a review of the debate and empirical evidence. *Health Expectations*, 5: 210-222.
- Schwartz, D., Lellouch, J. (1967). Explanatory and Pragmatic Attitudes in Therapeutical Trials. *Journal of Chronic Diseases* 20, 637–648.
- Science Media Centre (2025). *Expert reaction to announcement on UK-US pharmaceuticals deal and changes to NICE's cost-effectiveness thresholds*. December 1, 2025. London: Science Media Centre. *https://www.sciencemediacentre.org/expert-reaction-to-announcement-on-uk-us-pharmaceuticals-deal-and-changes-to-nices-cost-effectiveness-thresholds/*; last accessed February 20, 2026.

- Scriba, P.C., Middeke, M. (2007). Was das IQWiG besser machen (können) sollte. *Deutsche Medizinische Wochenschrift*, 132: 137-138.
- Sebastian, T., Toseef, M.U., Kurtz, M., Frost, H.M. (2023). Nasopharyngeal rapid diagnostic testing to reduce unnecessary antibiotic use and individualize management of acute otitis media. *Antimicrobial Stewardship & Healthcare Epidemiology*, 3 (1): e49. Doi: 10.1017/ash.2023.127.
- Sen A.K. (1980). Equality of What? In: McMurrin, S.M. (ed.) *The Tanner Lectures on Human Values*, Vol. 1, Cambridge, MA: Cambridge University Press.
- Sen A.K. (1985). *Commodities and Capabilities*. Amsterdam, North Holland.
- Sen A.K. (1987). *On Ethics and Economics*. Oxford: Blackwell Publishers.
- Sen A.K. (1993). Capability and well-being. In: Nussbaum, M.C., Sen, A.K. (Editors) *The Quality of Life*. Oxford: Clarendon Press: 31-53.
- Sen A. (2001). *Why Health Equity?* Keynote Address to Third International Conference on The Economics of Health: Within and Beyond Health Care. York, England, July 23, 2001.
- Sen A. (2002). Why health equity? *Health Econ.*, 11 (8): 659-666.
- Shah, B.K., Armaly, J., Swieter, E. (2017). Impact of parental cancer on children. *Anticancer Research*, 37: 4025–4028.
- Shah K.K. (2009). Severity of illness and priority setting in healthcare: a review of the literature. *Health Policy* 93, 77–84.
- Shetty, A., Lee, M., Valenyuela, J., Saab, S. (2024). Cost effectiveness of hepatitis C direct acting agents. *Expert Review of Pharmacoeconomics & Outcomes Research*, 24 (5): 589-597.

- Shields, G.E., Wilberforce, M., Clarkson, P., Farragher, T., Verma, A., Davies, L.M. (2022). Factors limiting subgroup analysis in cost-effectiveness analysis and a call for transparency. *PharmacoEconomics*, 40: 149-156.
- Simonati, A., Williams, R.E. (2022). Neuronal Ceroid Lipofuscinosis: The Multifaceted Approach to the Clinical Issues, an Overview. *Frontiers in Neurology*, 13: 811686. Doi: 10.3389/fneur.2022.811686.
- Sinclair, J.M.A., Gray, A., Rivero-Arias, O., Saunders, K.E.A., Hawton, K. (2011). Healthcare and social services resource use and costs of self-harm patients. *Soc Psychiatry Psychiatr Epidemiol*, 46: 263–271.
- Sinclair S. (2021). How to avoid unfair discrimination against disabled patients in healthcare resource allocation. *Journal of Medical Ethics*, 38: 158-159.
- Sinclair S. (2022). Explaining rule of rescue obligations in healthcare allocation: allowing the patient to tell the right kind of story about their life. *Medicine, Health Care and Philosophy*, 25: 31-46.
- Singer, P., McKie, J., Kuhse, H., Richardson, J. (1995). Double jeopardy and the use of QALYs in health care allocation. *Journal of Medical Ethics*, 21 (3): 144-150.
- Sloan F.A. (ed.) (1996). *Valuing Health Care – Costs, Benefits, and Effectiveness of Pharmaceuticals and Other Medical Technologies*. Cambridge, UK, New York, NY, and Melbourne, Vic: Cambridge University Press.
- Small D.A. (2015). On the Psychology of the Identifiable Victim Effect. In: Cohen, I.G., Daniels, N., Eyal, N. (eds.). *Identified versus Statistical Lives. An Interdisciplinary Perspective*. New York, N.Y.: Oxford University Press.

- Smith, R.D., Richardson, J. (2005). Can we estimate the 'social' value of a QALY? Four core issues to resolve. *Health Policy*, 74 (1): 77-84.
- Snyder H. (2019). Literature Review as a Research Methodology: An Overview and Guidelines. *Journal of Business Research*, 104: 333-339.
- Soley-Bori, M., Ashworth, M., Bisquera, A., Dodhia, H., Lynch, R., Wang, Y., Fox-Rushby, J. (2020). Impact of multimorbidity on healthcare costs and utilisation: a systematic review of the UK literature. *The British Journal of General Practice*, 71 (702): e39–e46.
- Špacírová, Z., Rejon-Parrilla, J.C., Espín, J. (2026). The complex price setting and reimbursement of non-industrial advanced therapy medicinal products. *Health Economics Review*. https://doi.org/10.1186/s13561-026-00732-0; last accessed March 10, 2026.
- Stadler, M., Schlander, M., Braeckman, M., Nguyen, T., Boogaerts, J.G. (2004). A cost-utility and cost-effectiveness analysis of an acute pain service. *Journal of Clinical Anesthesia*, 16: 159-167.
- Steuten L. (2026). *Your bar or mine? The bar for change versus the status quo in defining appropriate benefits for economic evaluation of health care technologies. Letter of Dissent, March 2026*, in response to McQueen et al. (2026). Defining Appropriate Benefits for Economic Evaluation of Health Care Technologies. Health Economics Methods Advisory Group. *https://hemamethods.org/wp-content/uploads/2026/03/HEMA-Report_For-Publication_031126.pdf*; last accessed March 26, 2026.
- Stolk, E.A., Busschbach, J.J., Caffa, M., Meuleman, E.J.H, Rutten, F.F.H. (2000a). Cost utility analysis of sildenafil

compared with papaverine-phentolamine injections. *British Medical Journal*, 320: 1165–1168.

- Stolk, E.A., Busschbach, J.J., Caffa, M., Meuleman, E.J.H, Rutten, F.F.H. (2000b). The obvious cost-effectiveness of sildenafil calls for a political discussion, not a technical one. Rapid Response to *British Medical Journal*, 320: 1156. *https://www.bmj.com/rapid-response/2011/10/28/obvious-cost-effectiveness-sildenafil-calls-political-discussion-not-techn*; last accessed Sept. 12, 2025.
- Strohmaier, C., Zechmeister-Koss, I. (2024). *Threshold values in health economic evaluations and decision-making. AIHTA Report No. 163*. Vienna: HTA Austria – Austrian Institute for Health Technology Assessment GmbH.
- Suzuki, R. Mori, T., Hachisuka, S., Okubo, Yamamoto, N., Nishikawa, H., Onaka, M., Yoshida, S., Kitano, T. (2025). Change of pediatric quality of life following inactivated influenza vaccination using EuroQol-5 dimensions-youth. *Journal of Infection and Chemotherapy*, 32(1): 102890. Doi: 10.1016/j.jiac.2025.102890.
- Swan, J.S., Sainfort, F., Lawrence, W.F., Kuruchittam, V., Kongnakorn, T., Heisey, D.M. (2003). Process utility for imaging in cerebrovascular disease. *Academic Radiology*, 10: 266-274.
- Swan, J.S., Lawrence, W.F., Roy, J. (2006). Process utility in breast biopsy. *Medical Decision Making*, 26 (4): 347-359.
- Swan, J.S., Kong, C.Y., Lee, J.M., Itauma, O., Halpern, E.F., Lee, P.A., Vavinskiy, S., Williams, O., Zoltick, E.S., Donelan, K. (2013). Patient and societal value functions for the testing morbidities index. *Medical Decision Making*, 33 (6): 819-838.
- Taylor, K., Batteson, R., Critchlow, S. (2025). *NICE decision-making ICER threshold analysis.* Delta Hat, May 2025.

https://www.abpi.org.uk/media/x3md0bwu/delta-hat_nice-icer-threshold-report-may-2025.pdf; last accessed June 20, 2025.

- Tengs, T.O., Meyer, G., Siegel, J.E., Pliskin, J.S., Graham, J.D., Weinstein, M.C. (1996). Oregon's Medicaid rankings and cost-effectiveness: Is there any relationship? *Medical Decision Making* 16: 99-107.
- Tersman F. (1993). *Reflective Equilibrium: An Essay in Moral Epistemology*. Stockholm, Sweden: Almqvist & Wiksell International.
- Timmins N. (2009). The NICE way of influencing health spending: a conversation with Sir Michael Rawlins. *Health Affairs (Millwood)*, 28 (5): 1360-1365.
- Timmins, N., Rawlins, M., Appleby, J. (2017). A Terrible Beauty: A short history of NICE the National Institute for Health and Care Excellence. *F1000Research*, 6, 915.
- Tobin J. (1970). On limiting the domain of inequality. *Journal of Law & Economics*, 13 (2): 263-277.
- Torraco R.J. (2005). Writing Integrative Literature Reviews: Guidelines and Examples. *Human Resource Development Review*, *4*(3): 356-367.
- Torrance, G.W., Feeny, D. (1989). Utilities and quality-adjusted life years. *International Journal of Technology Assessment in Health Care*, 5 (4): 559-575.
- Torrance, G.W., Thomas, W.H., Sackett, D.L. (1972). A utility maximization model for evaluation of health care programs. *Health Services Research*, 7: 118-133.
- Towse, A., Pritchard, C. (2002). National Institute of Clinical Excellence (NICE): is economic appraisal working? *Pharmacoeconomics*, 20 (Suppl. 3): 95-105.
- Towse, A., Pritchard, C., Devlin, N. (2002). *Cost-Effectiveness Thresholds: Economic and Ethical Issues*. London: King's Fund and Office of Health Economics.

- Tran, P.B., Kazibwe, J., Nikolaidis, G.F., Linnosmaa, I., Rijken, M., van Olmen, J. (2022). Costs of multimorbidity: a systematic review and meta-analyses. *BMC Medicine*, 20 (1): 234.
- Trouiller, J.-B., Laramée, P. (2023). Comparative assessment of reimbursement recommendations by NICE and HAS for oncology new medicines indicated for the treatment of solid tumors from 2015 to 2021. *Medical Decision Making*, 43 (7-8): 961-972.
- Trowman, R., Chung, H., Longson, C., Littlejohns, P., Clark, P. (2011). The National Institute for Health and Clinical Excellence and its role in assessing the value of new cancer treatments in England and Wales. *Clinical Cancer Research*, 17 (15): 4930–4935.
- Turkstra, E., Bettington, E., Donohue, M.L., Mervin, M.C. (2017). Pharmaceutical Benefits Advisory Committee recommendations in Australia. *International Journal of Technology Assessment in Health Care*, 33: 521–528.
- Ubel P.A. (2000). *Pricing life – why it's time for health care rationing*. Cambridge, MA: The MIT Press.
- Ubel, P.A., Loewenstein, G, Scanlon, D, Kamlet, M. (1996a). Individual utilities are inconsistent with rationing choices: A partial explanation why Oregon's cost-effectiveness list failed. *Medical Decision Making* 16 (2), 108-116.
- Ubel, P.A., DeKay, M.L., Baron, J., Asch, D.A. (1996b). Cost-effectiveness analysis in a setting of budget constraints – is it equitable? *New England Journal of Medicine*, 334 (18): 1174–1177.
- Ubel, P.A., Hirth, R.A., Chernew, M.E., Fendrick, A.M. (2003). What is the price of life and why doesn't it increase at the rate of inflation? *Archives of Internal Medicine*, 163: 1637–1641.

- United Nations (1948). *Universal Declaration of Human Rights*. G. A. Res. 217A (III), UN GAOR, Res. 71, UN Doc. A/810. New York, N.Y.: United Nations.
- United States Department of Health and Human Services (HHS) (2009). [FDA Center for Drug Evaluation and Research, US Department of Health and Human Services, FDA Center for Biologics Evaluation and Research, US Department of Health and Human Services FDA Center for Devices and Radiological Health.] *Guidance for industry, patient reported outcome measures: use in medical product development to support labeling claims. December, 2009. https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf*; accessed July 26, 2023.
- Upadhyaya S. (2025). NICE's highly specialized technologies (HST) criteria: a summary and impact analysis. *Rare Revolution Magazine*, May 14, 2025. *https://rarerevolutionmagazine.com*; last accessed July 07, 2025.
- Valderas, J.M., Alonso, J. (2008). Patient reported outcome measures: a model-based classification system for research and clinical practice. *Quality of Life Research*, 17 (9); 1125-1135.
- Vallejo-Torres, L., García-Lorenzo, B., Castilla, I., Valcárcel-Nazco, C., García-Pérez, L., Linertová, R., Polentinos-Castro, E., Serrano-Aguílar, P. (2016). On the estimation of the cost-effectiveness threshold: why, what, how? *Value in Health*, 19: 558-566.
- Vallejo-Torres, L., García-Lorenzo, B., Serrano-Aguilar, P. (2018). Estimating a cost-effectiveness threshold for the Spanish NHS. *Health Economics*, *27*(4), 746–761.
- Vallejo-Torres, L. García-Lorenzo, B., Edney, L.C., Stadhouders, N., Edoka, I., Castilla-Rodríguez, I., García-Pérez, L., Linertová, R., Valcárcel-Nazco, C., Karnon, J.

(2022). Are estimates of the health opportunity cost being used to draw conclusions in published cost-effectiveness analyses? A scoping review in four countries. *Applied Health Economics and Health Policy*, 20: 337-349.

- Vallejo-Torres, L., Claxton, K., Edney, L.C., Karnon, J., Lomas, J., Ochalek, J., Paulden, M., Stadhouders, N., Vanness, D.J. (2023). Challenges of calculating cost-effectiveness thresholds. *Lancet Global Health*, 11 (10): e1508. Doi: 10.1016/S2214-109X(23)00351-0.
- Vallejo-Torres, L., Edney, L.C., Espimnosa, O., Karnon, J., Longo, F., Paulden, M., Howdon, D., Vanness, D.J. (2026). Politicised changes to the NICE threshold risk making cost-effectiveness analysis performative, not informative. *Applied Health Economics and Health Policy*, 24: 243-246.
- Vancoppenolle, J., Franzen, N., Azarang, L., Juslin, T., Krini, M., Lubbers, T., Mattson, J., Mayeur, D., Menezes, R., Schmitt, J., Scotte, F., Seoane López, O., Skaali, T., Ubels, J., Schlander, M., Retel, V., van Harten, W.H., on behalf of OECI Working Group Health Economics. (2025). Financial toxicity and socioeconomic impact of cancer in Europe. *ESMO Open*, 10 (6): 105293.
- Vargas, C., De Abreu Lourenco, R., Espinoza, M., Goodall, S. (2025). Systematic literature review of access pathways to drugs for patients with rare diseases. *Applied Health Economics and Health Policy*, 23: 209-229.
- Ver Hoeve, E.S., Ali-Akbarian, L., Price, S.N., Lothfi, N.M., Hamann, H.A. (2021). Patient-reported financial toxicity, quality of life, and health behaviors in insured US cancer survivors. *Supportive Care in Cancer*, 29 (1): 349-358.
- Verweij M. (2015). How (not) to argue for the rule of rescue. Claims of individuals versus group solidarity. In: Cohen, I.G., Daniels, N., Eyal, N. (eds.). (2015). *Identified versus*

Statistical Lives. An Interdisciplinary Perspective. New York, N.Y.: Oxford University Press.

- Viscusi, W.K., Aldy, J.E. (2003). The value of a statistical life: a critical review of market estimates throughout the world. *Journal of Risk and Uncertainty*, 27: 5–76.
- Von Neumann, J., Morgenstern, O. (1944) *Theory of games and economic behavior*. Princeton, NJ: Princeton University Press.
- Wagle, J.A., Flacke, J.P., Knoerzer, D., Ruof, J., Merkesdal, S. (2021). Intraindividual comparisons to determine comparative effectiveness: their relevance for G-BA's Health Technology Assessments. *Value in Health*, 24 (5): 744-752.
- Walker, S., Sculpher, M., Drummond, M. (2011). The methods of cost-effectiveness analysis to inform decisions about the use of health care interventions and programs. In: Glied, S., Smith, P.C. (editors). *The Oxford Handbook of Health Economics*. Oxford and New York, NY: Oxford University Press, Chapter 31, pp. 733-758.
- Ward, L.M., Chambers, A., Mechichi, E., Wong-Rieger, D., Campbell, C. (2022). An international comparative analysis of public reimbursement of orphan drugs in Canadian provinces compared to European countries. *Orphanet Journal of Rare Diseases* 17: 113.
- Weinstein M.C. (1988). A QALY is a QALY is QALY – or is it? *Journal of Health Economics*, 7: 289-290.
- Weinstein M.C. (1990). Principles of cost-effective resource allocation in health care organizations. *Int J Technol Assess Health Care.*, 6 (1): 93-103.
- Weinstein, M.C., Stason, W.B. (1977). Foundations of cost-effectiveness analysis for health and medical practices. *N Engl J Med.*, 296 (13): 716-721.
- Weinstein, M.C., Zeckhauser, R. (1973). Critical ratios and efficient allocation. *J Public Econ.*, 2: 147-157.

- Weinstein, M.C., Torrance, G.W., McGuire, A. (2009). QALY: The Basics. *Value in Health* 12 (Suppl. 1): S5-S9.
- Whittemore, R., Knafl, K. (2005). The integrative review: updated methodology. *Journal of Advanced Nursing*, *52* (5): 546–553.
- Whyle, E.B., Olivier, J. (2021) Towards an Explanation of the Social Value of Health Systems: An Interpretive Synthesis. *International Journal of Health Policy and Management*, 10 (7): 414-429.
- Williams A. (1985a). The Economics of Coronary Artery Bypass Grafting. *British Medical Journal*, 291: 326-329.
- Williams A. (1985b). The value of QALYs. *Health and Social Service Journal*, 94 (4957 Suppl): 3-5.
- Williams A. (2004). *What could be nicer than NICE?* London: Office of Health Economics.
- Williams, J.S., Egede, L.E. (2016). The association between multimorbidity and quality of life, health status and functional disability. *American Journal of the Medical Sciences*, 352 (1): 45-52.
- Wilson, I.B., Cleary, P.D. (1995). Linking clinical variables with health-related quality of life—a conceptual model of patient outcomes. *Journal of the American Medical Association (JAMA)*, 273: 59–65.
- Wilson, N., Davies, A., Brewer, N., Nghiem, N., Cobiac, L., Blakely, T. (2019). Can cost-effectiveness results be combined into a coherent league table? Case study from one high-income country. *Population Health Metrics*, 17: 10.
- Wong, G., Greenhalgh, T., Westhorp, G., Buckingham, J., Pawson, R. (2013). RAMESES publication standards: meta-narrative reviews. *BMC Medicine*, *11*: 20.
- Woods, B., Revill, P., Sculpher, M, Claxton, K. (2016). Country-Level Cost-Effectiveness Thresholds: Initial

Estimates and the Need for Further Research. *Value in Health*, 19 (8): 929–935.

- World Health Organization, WHO [Commission on Macroeconomics and Health] (2001). *Macroeconomics and health: investing in health for economic development/report of the Commission on Macroeconomics and Health.* Geneva: World Health Organization (WHO). https://apps.who.int/iris/handle/10665/42435; last accessed January 28, 2025.
- World Health Organization, WHO (2003a). *Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis*. Tan-Torres Edejer, T., Baltussen, R., Adam, T., Hutu Bessy, R., Acharya, A., Evans, D.B., Murray, C.J.L. (eds). Geneva: World Health Organization.
- World Health Organization, WHO (2003b). *Technology appraisal programme of the National Institute for Clinical Excellence. A review by WHO. June-July 2003*. Copenhagen: World Health Organization (WHO). www.nice.org.uk/Docref.asp?d=85797; last accessed June 30, 2004.
- World Health Organization, WHO (2015). *Using health technology assessment for universal health coverage and reimbursement systems.* Geneva: World Health Organization. https://cdn.who.int/media/docs/default-source/health-economics/hta_november_meeting_report_final.pdf?sfvrsn=710d2747_1&download=true; last accessed January 12, 2025.
- Wouterse, B., van Baal, P., Versteegh, M., Brouwer, W. (2023). The Value of Health in a Cost-Effectiveness Analysis: Theory Versus Practice. *Pharmacoeconomics*, 41 (6): 607-617.
- Yabroff, K.R., Dowling, E.C., Guy, G.P. Jr., Banegas, M.P., Davidoff, A., Han, X., Virgo, K.S., McNeel, T.S., Chawla, N., Blanch-Hartigan, D., Kent, E.E., Li, C., Rodriguez, J.L., de

Moor, J.S., Zheng, Z., Jemal, A., Ekwueme, D.U. (2016). Financial hardship associated with cancer in the United States: findings from a population-based sample of adult cancer survivors. *Journal of Clinical Oncology*, 34 (3): 259–267.

- Yang, Y.T., Mahon, M.M. (2012). Palliative care for the terminally ill in America: the consideration of QALYs, costs, and ethical issues. *Medicine, Health Care, and Philosophy*, 15 (4): 411-416.
- Yerramilli, P., Fernández, Ó., Thomson, S. (2018). Financial protection in Europe: a systematic review of the literature and mapping of data availability. *Health Policy*, 122: 493–508.
- Zafar, S.Y., Abernethy, A.P. (2013). Financial toxicity, part I: a new name for a growing problem. *Oncology*, 27 (2): 80–81, 149.
- Zamora, B., Maignen, F., O'Neill, P., Mestre-Ferrandiz., J., Garau, M. (2019). Comparing access to orphan medicinal products in Europe. *Orphanet Journal of Rare Diseases*, 14, 95: *https://doi.org/10.1186/s13023-019-1078-5*.
- Zimmermann, B.M., Eichinger, J., Baumgartner, M.R. (2021). A systematic review of moral reasons on orphan drug reimbursement. *Orphanet Journal of Rare Diseases*, 16, 292: 1-21.

Appendix:
Literature Search - Figures & Tables

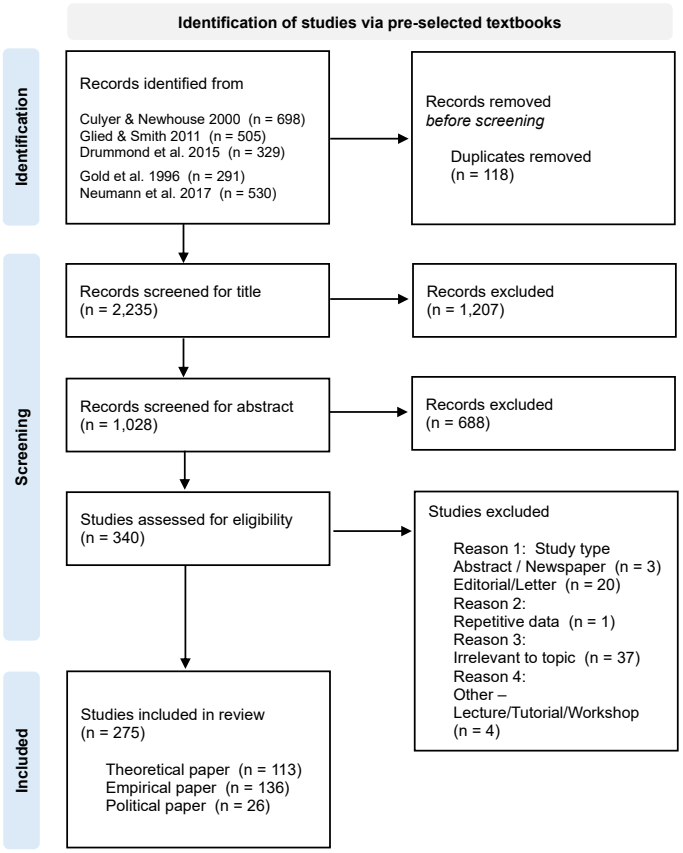


Figure A1: PRISMA flow diagram textbook search
(Source: Page et al., 2021)

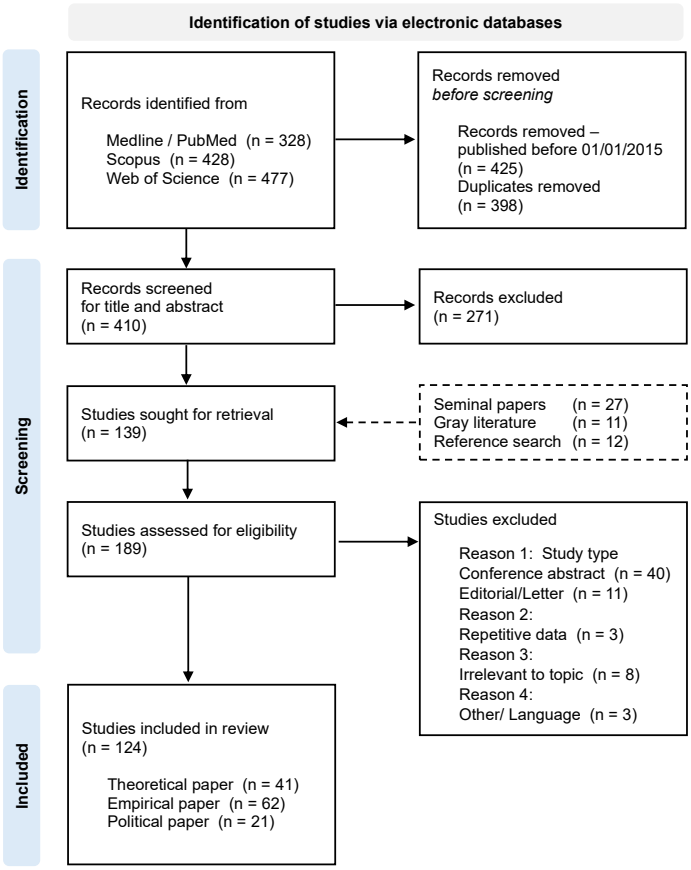


Figure A2: PRISMA flow diagram database search including seminal/defining papers and gray literature.
(Source: Page et al., 2021)

IV

Table A1: Search strings for electronic databases

Medline / PubMed
("marginal cost"[Title] OR "opportunity cost"[Title] OR "threshold*"[Title]) AND ("CEA"[Title/Abstract] OR "ICER"[Title/Abstract] OR "cost-effectiveness"[Title/Abstract] OR "WTP"[Title/Abstract] OR "willingness to pay"[Title/Abstract] OR "HTA"[Title/Abstract] OR "health technology assessment"[Title/Abstract] OR "QALY"[Title/Abstract] OR "quality-adjusted life year"[Title/Abstract])
Scopus
(TITLE ("marginal cost") OR TITLE ("opportunity cost") OR TITLE ("threshold*")) AND (TITLE-ABS ("ICER") OR TITLE-ABS ("CEA") OR TITLE-ABS ("cost-effectiveness") OR TITLE-ABS ("WTP") OR TITLE-ABS ("willingness to pay") OR TITLE-ABS ("HTA") OR TITLE-ABS ("health technology assessment") OR TITLE-ABS ("QALY") OR TITLE-ABS ("quality-adjusted life year"))
Web of Science (WoS)
(((TI[Title]=("marginal cost")) OR TI=("opportunity cost")) OR TI=("threshold*")) AND (((((((((TS[TopicSearch]=("ICER")) OR TS=("CEA")) OR TS=("cost-effectiveness")) OR TS=("WTP")) OR TS=("willingness to pay")) OR TS=("HTA")) OR TS=("health technology assessment")) OR TS=("QALY")) OR TS=("quality-adjusted life year"))

CEA, cost effectiveness analysis; HTA, health technology assessment; ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; WTP, willingness to pay.

Table A2: Articles assessed for eligibility criteria

Articles retrieved from	Exclusion criteria
Textbook search	Studies not referenced in pre-selected textbooks/ textbook chapters Conference abstracts Newspaper articles Editorials and/or letters [Empirical] Studies with repetitive/ secondary data Studies irrelevant to understand the use of thresholds in the context of CEA & HTA/ health care decision making Data from lectures/ tutorials/ workshops Non-English language studies
Database search	Published before January 2015 Published after August 2024 Conference abstracts Editorials and/or letters [Empirical] Studies with repetitive/ secondary data Studies irrelevant to understand the use of thresholds in the context of CEA & HTA/ health care decision making Non-English language studies

CEA, cost effectiveness analysis; HTA, health technology assessment.

IV

Glossary of Acronyms

ADA	Americans with Disabilities Act
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
A4R	Accountability for Reasonableness
AIDS	Acquired immune deficiency syndrome
AIFA	Agenzia Italiana del Farmaco
AUS-$	Australian Dollar
BIA	Budget Impact Analysis
CADTH	Canadian Agency for Drugs and Technologies in Health
CDA-AMC	Canada´s Drug Agency – L'Agence des médicaments du Canada
CAN-$	Canadian Dollar
CCG	Clinical Commissioning Group
CDF	Cancer Drugs Fund
CEA	Cost effectiveness analysis
CET	Cost effectiveness threshold
DALY	Disability-adjusted life year
EMA	European Medicines Agency
EoL	End-of-life
EU	European Union
EUR / €	Euro
FDA	Food and Drug Administration
GBP / £	Great British Pound
GDP	Gross domestic product
HAS	Haute Autorité de Santé
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio

IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
LSDP	Life Saving Drugs Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OHP	Oregon Health Plan
OMP	Orphan medicinal product
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCORI	Patient-Centered Outcomes Research Institute
PCT	Primary Care Trust
QALDs	Quality-adjusted life days
QALMs	Quality-adjusted life months
QALYs	Quality-adjusted life years
R&D	Research & Development
RoR	Rule of rescue
TLR	Time-limited recommendation
TLV	Tandvårds- och läkemedelsförmånsverket
UK	United Kingdom
U.S.	United States
US-$	United States Dollar
VSLY	Value of a statistical life year
WHO	World Health Organization
WHO-CHOICE	WHO – "Choosing Interventions that are Cost-Effective"
WTP	Willingness to pay

IV

© INNOVALHC • Wiesbaden 2026
ISBN 978-3-941609-38-9

Discussion Paper Series Editors:
Michael Schlander and Oliver Schwarz

INNOVALHC
Institute for Innovation & Valuation in Health Care
Institut für Innovation & Evaluation im Gesundheitswesen e.V.

Prof. Dr. Michael Schlander (Chairman)
Prof. Dr. Oliver Schwarz (Vice Chairman)
Prof. Dr. G.-Erik Trott (Vice Chairman)

Official Site: Luitpoldstraße 2-4 • D-63739 Aschaffenburg
Registered at Vereinsregister Aschaffenburg VR 1371

Recognized officially as a not-for-profit organization by
(*als gemeinnützig anerkannt vom*) Finanzamt Aschaffenburg

Office Address: An der Ringkirche 4 • D-65197 Wiesbaden (Germany)

www.innoval-hc.com

Cover: Railroad Tracks by Manfred Richter.
Photograph © Pixabay; free for use (2026).

Discussion Paper

No. 39

November 2026

INNOVAL HC
Institute for Innovation & Valuation in Health Care