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Valuing the Societal Impact of Medicines and Other Health Technologies: A User Guide to Current Best Practices

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Abstract: This study argues that value assessment conducted from a societal perspective should rely on the Generalized Cost-Effectiveness Analysis (GCEA) framework proposed herein. Recently developed value assessment inventories – such as the Second Panel on Cost-Effectiveness's "impact inventory" and International Society of Pharmacoeconomics Outcomes Research (ISPOR) "value flower" – aimed to more comprehensively capture the benefits and costs of new health technologies from a societal perspective. Nevertheless, application of broader value elements in practice has been limited in part because quantifying these elements can be complex, but also because there have been numerous

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methodological advances since these value inventories have been released (e.g. generalized and risk-adjusted cost effectiveness). To facilitate estimation of treatment value from a societal perspective, this paper provides an updated value inventory – called the GCEA value flower – and a *user guide* for implementing GCEA for health economics researchers and practitioners. GCEA considers 15 broader value elements across four categories: (i) uncertainty, (ii) dynamics, (iii) beneficiary, and (iv) additional value components. The uncertainty category incorporates patient risk preferences into value assessment. The dynamics category petals account for the evolution of real-world treatment value (e.g. option value) and includes drug pricing trends (e.g. future genericization). The beneficiary category accounts for the fact health technologies can benefit others (e.g. caregivers) and also that society may care to whom health benefits accrue (e.g. equity). Finally, GCEA incorporates additional broader sources of value (e.g. community spillovers, productivity losses). This GCEA user guide aims to facilitate both the estimation of each of these value elements and the incorporation of these values into health technology assessment when conducted from a societal perspective.

Keywords: generalized cost-effectiveness analysis; health technology assessment; cost-effectiveness analysis; value assessment

1 Executive Summary

Recently developed value assessment inventories aimed to better capture the benefits and costs of health technologies. In 2016, the Second Panel on Cost-Effectiveness recommended best practices for value assessment, including the consideration of a societal perspective and novel value elements, such as productivity costs and future costs (Sanders et al. 2016a). In 2018, an International Society of Pharmacoeconomics Outcomes Research (ISPOR) special task force developed the ISPOR Value Flower, which described an inventory of value elements traditionally excluded from cost-effectiveness analyses (Lakdawalla et al. 2018). The National Institute for Health and Care Excellence (NICE) has introduced value adjustments based on disease severity and magnitude of clinical benefit (Excellence 2022a). More recently, the concept of Generalized Cost-effectiveness analysis (GCEA) was proposed to incorporate ISPOR Value Flower elements into Medicare drug price negotiations under the Inflation Reduction Act (Padula and Kolchinsky 2024). Yet, health technology assessment (HTA) bodies still remain hesitant to incorporate recent methodological advances into value assessment, frequently citing implementation challenges (Breslau et al. 2023). For example, ICER's 2023

updated value assessment framework cites these challenges and elected to not incorporate Generalized and Risk-Adjusted Cost Effectiveness (GRACE) or dynamic drug pricing into their framework, although it did remain open to considering these approaches in the future ("Value Assessment Framework" 2023).

Researchers face two fundamental challenges when integrating novel or broader value elements into their cost-effectiveness models. First, quantifying these elements can be complex, and some question how they affect current cost-effectiveness thresholds. The literature mainly offers either broad, high-level overviews or a highly detailed application for quantifying a single value element in isolation (Asaria et al. 2015; Excellence 2022b; Lakdawalla et al. 2012, 2018; Landfeldt et al. 2018; Lee et al. 2021, 2022; Longacre et al. 2018; Maguire and Maguire 2020; Hernandez et al. 2022; Neumann et al. 2001; Pauly et al. 2002; Pritchard and Sculpher 2000; Shafrin and Venkatachalam 2020; Shafrin et al. 2017, 2021, 2022; Thornton Snider et al. 2018; Yang et al. 2021; Zhang et al. 2011). Conceptual papers, while accessible to a wider audience, provide limited guidance on how to estimate or include elements within value assessments without double-counting. On the other hand, complex case studies may be highly technical and relevant to only a single case study and thus may be challenging for practitioners to implement (Drupp et al. 2018; Frankel et al. 2023; Lakdawalla and Phelps 2021, 2022; Li et al. 2019; Love-Koh et al. 2019). Second, there have been significant methodological advancements since the ISPOR Value Flower's development. The GRACE model introduced in 2020 aims to incorporate patient risk preferences, disease severity, insurance value, and diminishing marginal returns within value assessment (Lakdawalla and Phelps 2021, 2022). Numerous studies have developed methods to estimate option value both *ex ante* and *ex-post* (Becker, Murphy, and Philipson 2007; Lee et al. 2022; Li and Garrison 2020; Thornton Snider et al. 2018). Other literature has incorporated dynamic drug pricing (Cohen 2023; Garrison Jr, Jiao, and Dabbous 2023). Finally, more studies reflect the value of reduced health disparities by using approaches like distributional cost-effectiveness (DCEA) (Kowal et al. 2023).

This white paper provides a *user guide* for implementing GCEA to include broader value elements into cost-effectiveness models to value a drug's total societal impact. Here, "generalized" refers to inclusion of all societal cost and benefits and to build on previous unifying value inventories (e.g. ISPOR, Second Panel). This study is distinct from the World Health Organization's GCEA, which advocates for consideration of conventional CEA models aligned with regional, national, or sectional contexts (Hutubessy et al. 2003). While our GCEA incorporates value elements (or "petals") beyond those in the ISPOR Special Task Force's "augmented CEA", it organizes them into four categories: uncertainty, dynamics, beneficiary, and additional value components. The uncertainty category aims to move beyond the outcomes for

the average or median patient by also considering the distribution of outcomes and how changes in uncertainty may impact patient well-being. The uncertainty category petals include outcome certainty (which combines the "value of reducing outcome uncertainty" and "value of hope"), disease risk reduction (previously referenced as "insurance value"), and the value of knowing (for diagnostics). Dynamics category petals account for the evolution of real-world treatment value and includes drug pricing trends, particularly due to genericization, changes in disease prevalence, option value, scientific spillover, and different societal rates of discounting. The beneficiary category accounts for the fact that value can vary depending on who is benefiting. Measuring patient-centered health improvements using GRACE to account for disease severity is a starting point, but many value assessment bodies also want to incorporate health equity, and family and caregiver spillover. Finally, GCEA incorporates additional broader sources of value, including community spillover, patient productivity losses, adherence-improving factors, and direct non-medical costs of illness (Figure E.1).

This paper provides guidelines for calculating each petal in practice. For each petal, this white paper explains what it represents and why that value is unique and describes the petal's computation. For select examples, this white paper also provides best practice guidance, empirical applications, and numerical examples. Table E.1 provides a checklist practitioners can use to describe which GCEA petals were incorporated into their evaluation and how each petal was measured. This checklist could be added to cost effectiveness analysis manuscripts to help journal reviewers and readers understand which value petals were and were not included in the evaluation. It is important to note that the GCEA value flower could evolve with future methodological advances to include new value elements.

Value assessments provide signals and insights about the potential value of innovative medicines in healthcare decision-making, at their best complementing the societal and stakeholder preferences revealed by markets. A thorough appreciation of the societal costs and benefits of innovative medicines is necessary to ensure that resources are efficiently allocated to those in need while preserving incentives for the continued innovation of medicines that offer yet more societal value. GCEA addresses the well-documented limitations of conventional CEA and provides a holistic approach to pave the way forward. This user guide provides practical suggestions based on consensus from leading researchers on how modelers, economists, and value assessors can estimate and incorporate each value element into value assessments. In specific assessment, we recommend value assessors examine each value element for relevance to the specific innovation and indication, incorporate the relevant ones when feasible, and speak to limitations that precluded a relevant

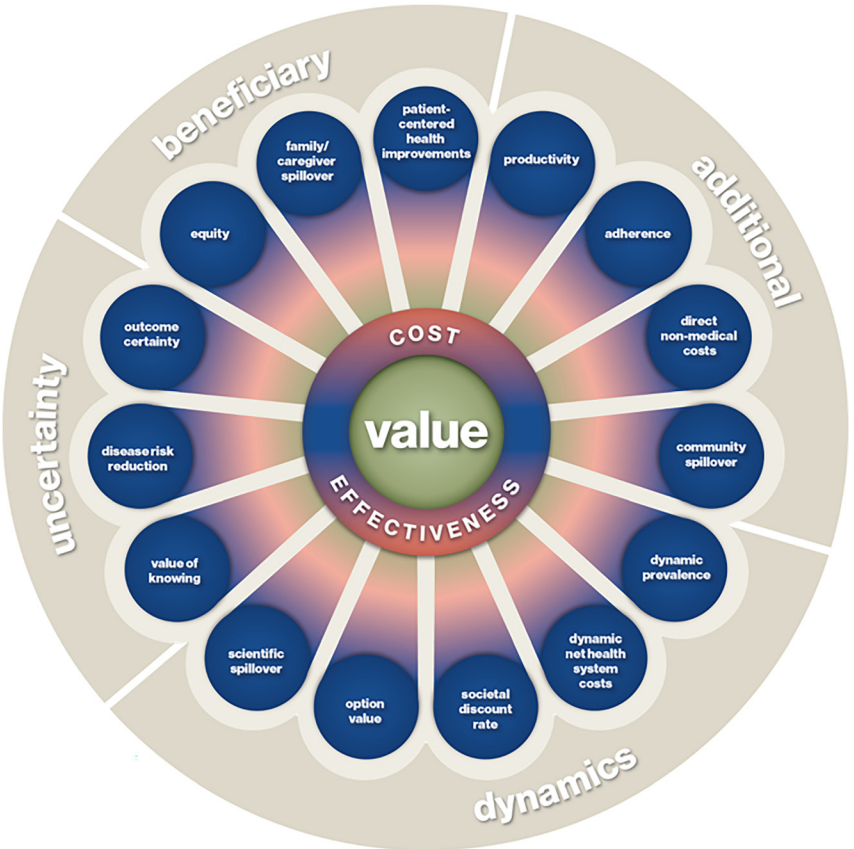

Figure E.1: GCEA value flower.

elements inclusion. By putting GCEA into standard practice in value assessment, we can continue to advance the methods and ensure that we are maximizing the welfare for our current and future generations.

This paper is structured as follows. The introduction provides the background, rationale, and motivation for incorporating novel or broader value elements and an overview of the GCEA Value Flower. The paper's body has four sections corresponding the four value categories: uncertainty, dynamics, beneficiary, and additional value components. Each section describes its component petals and recommends an empirical methodology (Table E.2). Next, a discussion addresses the implications, strengths, and limitations of GCEA, and future research needs. Finally, an appendix contains a series of numerical examples.

Table E.1: Generalized cost effectiveness analysis (GCEA) implementation petal checklist.

Category	Petal	Recommended Approaches	How measured in model: Base-case analysis	Sensitivity analysis	Contextual Consideration	Not relevant	Suggested parameterization**
Uncertainty	Outcome Certainty	**GRACE**	☐	☐	☐	☐	*Expo power utility, RRA: 0.282 [0.217, 0.349] (Mulligan et al. 2024)*
		Stated Preference Surveys	☐	☐	☐	☐	-
	Disease Risk Reduction	**GRACE**	☐	☐	☐	☐	*Expo power utility, RRA: 0.282 [0.217, 0.349] (Mulligan et al. 2024)*
		Stated Preference Surveys	☐	☐	☐	☐	-
	Value of Knowing	**Stated Preference Surveys**	☐	☐	☐	☐	-
Dynamics	Dynamic Net Health System Costs	**Dynamic Drug Pricing**	☐	☐	☐	☐	*2 times COGS for generic price (Sood et al. 2017) (may vary for biologics)*
		Stacked Cohort Models	☐	☐	☐	☐	*70 cohorts (Graf et al. 2023)*
	Dynamic Prevalence	**Cohorts Weighted by Annual Disease Incidence**	☐	☐	☐	☐	-
	Societal Discount Rate	**Real, Risk-Free Long-Term Interest Rate**	☐	☐	☐	☐	*1%-3% (Young 2023; Cohen 2024)*
		Ramsey Equation	☐	☐	☐	☐	-
	Option Value	**Ex-Ante**	☐	☐	☐	☐	*Approval probability: 32.0% (large molecule) 13.0% (small molecule) (DiMasi et al. 2010)*
		Ex-Post	☐	☐	☐	☐	-
	Scientific Spillover	Analysis of Possible Knowledge Spillovers *(e.g., quantifying therapeutic novelty and applicability to other disease areas)*	N/A	N/A	☐	☐	-
Beneficiary	Patient-Centered Health Improvements	**GRACE**	☐	☐	☐	☐	*Expo power utility, RRA: 0.282 [0.217, 0.349] (Mulligan et al. 2024)*
		Decision Modifiers	☐	☐	☐	☐	-
		Life Years (sensitivity only)	☐	☐	☐	☐	-
	Equity	**DCEA**	☐	☐	☐	☐	*Atkinson (Love-Koh et al. 2019): 10.95 Kolm (Love-Koh et al. 2019): 0.15*
	Family and Caregiver Spillover	**Caregiver Quality of Life**	☐	☐	☐	☐	-
		Caregiver Productivity	☐	☐	☐	☐	-
		Caregiver Costs *(i.e., medical, transportation, home renovation, and relocation costs)*	☐	☐	☐	☐	-
Additional Value Elements	Community Spillover	**Incorporate Impact on Those without Disease** *(e.g., fear of contagion for infectious disease)*	☐	☐	☐	☐	-
	Productivity	**Market Productivity Impacts**	☐	☐	☐	☐	*Include wages and benefits (Review 2023c)*
		Non-market Productivity Impacts	☐	☐	☐	☐	-
		Spillover Productivity Impacts	☐	☐	☐	☐	-
		Macroeconomic Impacts	☐	☐	☐	☐	-
	Adherence	**Model Impact of Adherence on Cost, Quality of Life and Effectiveness**	☐	☐	☐	☐	-
	Direct Non-Medical Costs	**Disease-specific, Direct Non-Medical Costs**	☐	☐	☐	☐	-

Approaches appearing in **blue** are the preferred methods of GCEA. GRACE = generalized and risk-adjusted cost-effectiveness; EP: Two-parameter expo-power utility function; COGS = cost of goods sold; DCEA = distributional cost-effectiveness analysis. *Suggested parameters from literature that can be used in the estimation of a given value component or method.

Table E.2: References to key figures and useful papers for GCEA implementation by GCEA petal.

GCEA Value category	GCEA value petal	Key figure or table to reference	Useful reference for implementation
Uncertainty	Outcome certainty	Figure 3	Lakdawalla and Phelps (2022)
	Disease risk reduction	Figure 4	Lakdawalla and Phelps (2022)
	Value of knowing	N/A	Phillips et al. (2006)
Dynamics	Dynamic net health system costs	Box 2, Figure 5, Tables 5 and 6	Cohen (2023) Garrison et al. (2023)
	Dynamic prevalence	Box 2 and Table 6	Lakdawalla and Phelps (2023)
	Option value	Box 3, Figure 7	Li et al. (2022)
	Scientific spillover	Box 4	Frankel et al. (2023)
	Societal discount rate	Box 5 and Table 7	Circular No. A-4 (2023) Cohen (2024)
Beneficiary	Patient centered health improvements	Table 8	Lakdawalla and Phelps (2022)
	Equity	Box 6	Yang et al. (2020)
	Family and caregiver spillover	Figure 8	Al-Janabi et al. (2016) Chiu et al. (2022)
Additional	Community spillover	Figure 9	Ma et al. (2020)
	Productivity	Box 7	Jiao and Basu (2023)
	Adherence	Box 8	Lakdawalla et al. (2018)
	Direct non-medical costs	N/A	Lakdawalla et al. (2018)

2 Introduction

In recent decades, innovations in medicine have greatly improved patient outcomes through the treatment and detection of both rare and common diseases. However, new health technologies often lead to increases in per capita healthcare spending. In response to these rising costs, diverse stakeholders – including both governmental and non-governmental organizations such as the Institute for Clinical and Economic Review (ICER), state prescription drug affordability boards, and the National Institute for Health and Care Excellence (NICE) – are using formal value assessment techniques in order to inform coverage and reimbursement/pricing decisions (Excellence 2022b; Review 2023a; Sklar and Robertson 2019). However, these health technology assessment (HTA) bodies traditionally focus on health gains and costs that accrue to the health care sector and may not incorporate the full range of impacts of new health technologies on society and on patients. While the reason for taking this narrow view of a medicine's cost effectiveness is typically that healthcare spending is finite and therefore spending on any new medicines necessarily comes at the expense of some other healthcare benefit, the

fact that nearly all nations have elected to spend more on healthcare over time suggests that societies look at resource allocation holistically and are willing to spend more on healthcare at the expense of other options across their entire economy. Therefore, to better understand those tradeoffs, it makes sense to appreciate the full value of an innovation to society.

In this paper, we provide the methods that can be used to capture the societal costs and benefits of a health technology within an HTA evaluation. This user's guide follows the calls from highly respected bodies to capture societal costs and benefits more broadly. For instance, the Second Panel on Cost-Effectiveness in Health and Medicine provided a list of recommendations, emphasizing the inclusion of a societal perspective reference case in cost-effectiveness analysis (CEA) and the consideration of consequences both inside and outside the formal healthcare sector (Sanders et al. 2016b). In 2018, the ISPOR Value Flower identified novel, non-trivial value components to incorporate into conventional CEA frameworks, and multiple studies have now provided empirical estimates of and substantiated these value components in isolation (Asaria et al. 2015; Excellence 2022b; Lakdawalla et al. 2012, 2018; Landfeldt et al. 2018; Lee et al. 2021, 2022; Longacre et al. 2018; Maguire and Maguire 2020; Hernandez et al. 2022; Neumann et al. 2001; Pauly et al. 2002; Pritchard and Sculpher 2000; Shafrin and Venkatachalam 2020; Shafrin et al. 2017; Shafrin et al. 2021, 2022; Thornton Snider et al. 2018; Yang et al. 2021; Zhang et al. 2011).

While measuring a health technology's full societal impact is gaining broad acceptance in theory, many researchers, modelers, and value assessors are unclear how to actually implement broader societal value elements in practice. In ICER's 2023 value assessment framework update, for instance, ICER discussed the potential need to incorporate certain ISPOR value flower elements as well as novel methods; however, ICER is not currently implementing many of these broader value elements, citing a variety of methodological challenges for quantifying them in practice (Review 2023c). NICE has attempted to implement broader value elements using "decision modifiers" based on disease severity and magnitude of treatment benefit (Excellence 2022b). While these decision modifiers are simple to implement, they are not grounded in economic theory and are largely implemented in a logically inconsistent manner. In 2020, Lakdawalla and Phelps developed the Generalized and Risk-Adjusted Cost Effectiveness (GRACE) model (Review 2023c). GRACE aims to incorporate patients' risk preferences and disease severity into value assessments and to move away from evaluations based solely on average outcomes. These and other initiatives have revealed concepts of value such as "insurance value," "value of hope," "option value," and others (Lakdawalla and Phelps 2020, 2021, 2022).

To help researchers more fully capture all benefits and costs to society, this white paper offers an easy-to-use guide for implementing generalized cost-effectiveness analysis (GCEA). GCEA is philosophically aligned with benefit cost analysis (BCA) in attempting to include all relevant costs and benefits when evaluating any intervention of interest (Lave 1996; Mishan and Quah 2020). We distinguish GCEA from conventional CEA in that GCEA always incorporates value from the societal perspective including issues around uncertainty, dynamics, patient-centered care, and other societal value elements (Padula and Kolchinsky 2024). While estimating every petal of GCEA would be ideal, time and resource constraints may make this infeasible; moreover, the impact of different GCEA petals on treatment petals is likely to vary across diseases and health technologies. Thus, cost analyses should be evaluated as appearing on a spectrum between a conventional CEA and a maximally generalized GCEA depending on how comprehensively it assesses value (Figures 1 and 2).

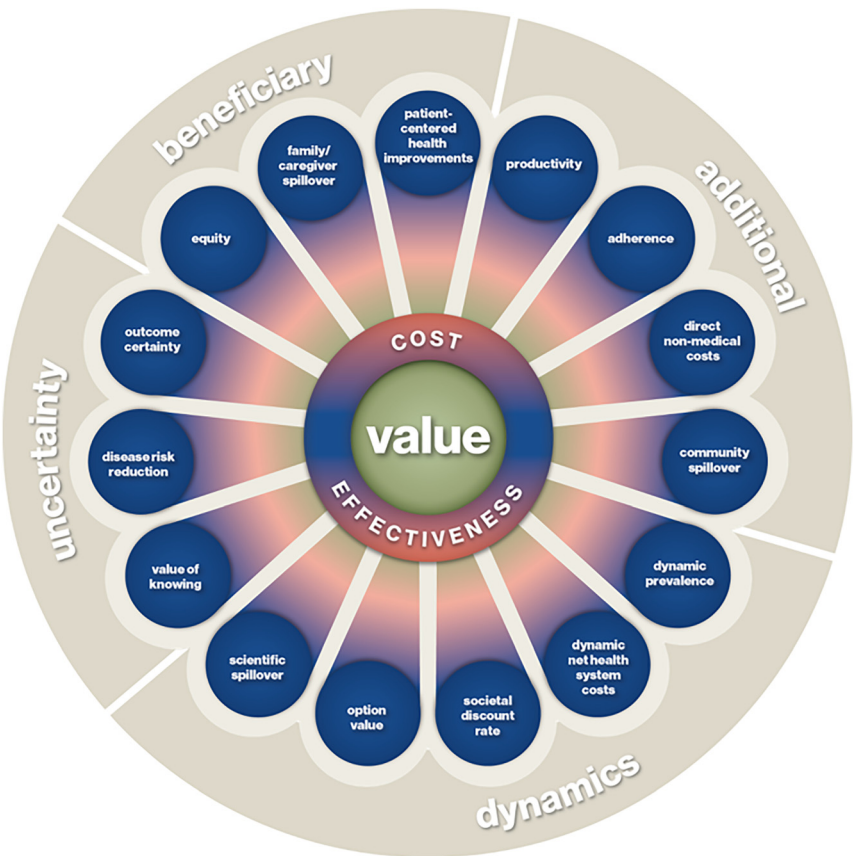

Figure 1: Generalized cost effectiveness value flower.

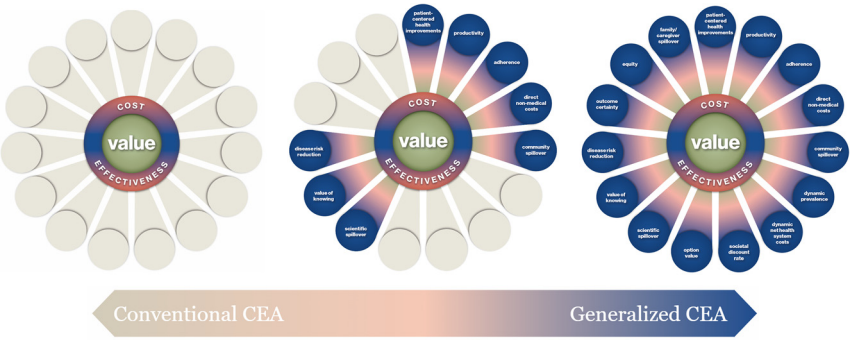

Figure 2: Evolution of the GCEA value flower.

The goal of the implementation guide is twofold. First, we enumerate the core value components using the GCEA value flower. The GCEA value flower can be considered an expanded version of the value flower developed by ISPOR. Second, this paper reviews each petal of the flower and explains (i) what the petal means and (ii) how researchers can implement it in practice. This white paper can be read both as a holistic white paper as well as a reference guide where researchers can pick the value component they are interested in quantifying and learn best practices for estimating it.

2.1 Generalized Cost-Effectiveness Analysis (GCEA) Value Flower

There have been multiple initiatives characterizing the GCEA value flower (Lakdawalla et al. 2018; Review 2023c; Sanders et al. 2016a). We categorize GCEA's petals into four groups: (i) uncertainty, (ii) dynamics, (iii) beneficiary, and (iv) additional elements (Figure 1). The elements of conventional CEA – including the use of conventional quality-adjusted life-years (QALYs) and the direct treatment costs and potential cost offsets –are captured by the core of the GCEA value flower; the GCEA flower with none of the current petals (i.e. just the pistil) would represent conventional CEA (Figures 1 and 2). Ideally, effectiveness would be measured in a patient-centered matter and could include both general health gains – which could be measured in QALYs – and potentially disease-specific measures of effectiveness which may be more or less difficult to convert into QALYs. Conventional healthcare costs and effectiveness as core value elements, however, are not discussed in this paper as our focus is expanding *beyond* conventional CEA.

2.1.1 Uncertainty

This category includes three petals recognizing the values associated with uncertainty of patient's future health outcomes borne by the stochastic natures of the treatment effectiveness and the development of disease (Table 1). *Outcome certainty* represents the value that risk-averse or risk-preferring patients place on the distribution of health outcomes independent of the expected value (value of reducing risk in health outcomes) as well as the potential for highly favorable outcomes enabled by treatment (value of hope).[1] *Disease risk reduction* represents potential health benefits to non-patients who might gain peace-of-mind that a treatment exists should they become sick (insurance value). There is another petal in this category not directly related to uncertainty on future health outcomes: *the value of knowing* represents the value of improved diagnostics, which facilitates more informed treatment decisions by reducing the uncertainty surrounding a patient's current health status. For each of these petals, the value beyond what would be accounted for in conventional CEA is largely driven by the degree of patient risk-aversion.

2.1.2 Dynamics

This category has five petals that account for how timing affects value (Table 1). *Dynamic net health system costs* accounts for how care costs change, as with the decline in a drug's price that typically accompanies the introduction of generic competition. *Dynamic disease prevalence* (or "dynamic prevalence" for brevity) accounts for how changes in a condition's prevalence affect treatment value (e.g. the expected increase in the prevalence of Alzheimer's disease accompanying the aging of the population, or the decline in the prevalence of a contagious disease that accompanies treatment). *Real option value* (or "option value" for brevity) represents the value of living long enough to take advantage of future innovations. *Scientific spillover* represents the value of expected innovation that a treatment's development will trigger. Finally, the *societal discount rate* informs the relationship between an outcome's value and how far in the future it occurs.

2.1.3 Beneficiary

The third category examines the beneficiaries of treatment value in more detail and considers cases where the value of new health technologies may vary depending on to whom the benefits accrue (Table 1). While conventional CEA focuses only on patients as a homogenous entity, patients with different baseline health allocations, patients

1 Outcome certainty includes the "value of hope" which was a distinct petal identified in the ISPOR Value Flower. See: (Lakdawalla et al. 2018).

Table 1: Generalized cost effectiveness analysis (GCEA) implementation petal checklist.

Category	Petal	Recommended Approaches	How Measured in Model: Base-case analysis	Sensitivity analysis	Contextual Consideration	Not relevant	Suggested Parameterization*
Uncertainty	Outcome certainty	**GRACE**	☐	☐	☐	☐	*Expo power utility, RRA: 0.282 [0.217, 0.349]* (Mulligan et al. 2024)*
		Stated Preference Surveys	☐	☐	☐	☐	-
	Disease Risk Reduction	**GRACE**	☐	☐	☐	☐	*Expo power utility, RRA: 0.282 [0.217, 0.349]* (Mulligan et al. 2024)*
		Stated Preference Surveys	☐	☐	☐	☐	-
	Value of Knowing	**Stated Preference Surveys**	☐	☐	☐	☐	-
Dynamics	Dynamic Net Health System Costs	**Dynamic Drug Pricing**	☐	☐	☐	☐	*2 times COGS for generic price (Sood et al. 2017) (may vary for biologics)*
		Stacked Cohort Models	☐	☐	☐	☐	*70 cohorts (Graf et al. 2023)*
	Dynamic Prevalence	**Cohorts Weighted by Annual Disease Incidence**	☐	☐	☐	☐	-
	Societal Discount Rate	**Real, Risk-Free Long-Term Interest Rate**	☐	☐	☐	☐	*1%-3% (Young 2023; Cohen 2024)*
		Ramsey Equation	☐	☐	☐	☐	-
	Option Value	**Ex-Ante**	☐	☐	☐	☐	*Approval probability: 32.0% (large molecule) 13.0% (small molecule) (DiMasi et al. 2010)*
		Ex-Post	☐	☐	☐	☐	-
	Scientific Spillover	Analysis of Possible Knowledge Spillovers *(e.g., quantifying therapeutic novelty and applicability to other disease areas)*	N/A	N/A	☐	☐	-
Beneficiary	Patient-Centered Health Improvements	**GRACE**	☐	☐	☐	☐	*Expo power utility, RRA: 0.282 [0.217, 0.349]* (Mulligan et al. 2024)*
		Decision Modifiers	☐	☐	☐	☐	-
		Life Years (sensitivity only)	☐	☐	☐	☐	-
	Equity	**DCEA**	☐	☐	☐	☐	*Atkinson (Love-Koh et al. 2019): 10.95 Kolm (Love-Koh et al. 2019): 0.15*
	Family and Caregiver Spillover	**Caregiver Quality-of-Life**	☐	☐	☐	☐	-
		Caregiver Productivity	☐	☐	☐	☐	-
		Caregiver Costs *(i.e., medical, transportation, home renovation, and relocation costs)*	☐	☐	☐	☐	-
Additional Value Elements	Community Spillover	**Incorporate Impact on Those without Disease** *(e.g., fear of contagion for infectious disease)*	☐	☐	☐	☐	-
	Productivity	**Market Productivity Impacts**	☐	☐	☐	☐	*Include wages and benefits (Review 2023c)*
		Non-Market Productivity Impacts	☐	☐	☐	☐	-
		Spillover Productivity Impacts	☐	☐	☐	☐	-
		Macroeconomic Impacts	☐	☐	☐	☐	-
	Adherence	**Model Impact of Adherence on Cost, Quality of Life and Effectiveness**	☐	☐	☐	☐	-
	Direct Non-Medical Costs	**Disease-specific, Direct Non-medical Costs**	☐	☐	☐	☐	-

Approaches appearing in **blue** are the preferred methods of GCEA. GRACE = generalized and risk-adjusted cost-effectiveness; EP: Two-parameter expo-power utility function; COGS = cost of goods sold; DCEA = distributional cost-effectiveness analysis. *Suggested parameters from literature that can be used in the estimation of a given value component or method.

representing disadvantaged groups, and caregivers all experience the benefits of medical innovation differently. Thus, this section defines which types of beneficiaries GCEA considers. *Patient-centered health improvements* examine how patient-level characteristics, such as permanent disability at baseline and disease severity, affect how society values identical magnitudes of health improvements. *Equity* acknowledges that while conventional CEA focuses on the health improvements of the average patient, in reality health benefits may be more highly valued if they also help to reduce current health disparities across patient subgroups (e.g. defined by socioeconomic status). Finally, *family and caregiver spillover* considers how treatments impact the well-being of friends and family members; for example, caring for a loved one often leads to caregiver burdens such as productivity loss, reduced quality of life, and indirect costs of care.

2.1.4 Additional Value Elements

Lastly, GCEA considers additional value elements including community spillover, patient productivity impacts, improved treatment adherence, and direct non-medical costs (Table 1). *Community spillover* measure the impact of disease on the broader communities that patients inhabit, including, for example, reduced fears of contagion. *Productivity* can be characterized as the reduction in losses of the market and non-market output as a consequence of treatment for the disease condition as well as spillover of these productivity impacts to the broader economy. *Adherence* effects add value to patients by providing innovative factors (e.g. less invasive mode of administration) that increase the likelihood that patients will take the treatment as prescribed and receive the full benefit of their treatment. Finally, there may be additional *direct non-medical costs* of a disease (e.g. installing wheelchair access in one's home, transportation costs) borne by certain patient populations that can be mitigated by medical innovations.

These elements of value could evolve with future methodological advances to include new value elements. However, at the time of this study these petals represent a best practice value inventory to wholistically capture the value of medical innovation.

2.2 GCEA Versus Previous Value Inventories

GCEA differs from previous efforts to make value assessment more comprehensive (Table 2). The Second Panel emphasized the importance of both the healthcare and societal perspectives (Sanders et al. 2016b). It also introduced an "impact inventory" that featured impacts on labor productivity and caregivers, which is also considered by the ISPOR value inventory (Lakdawalla et al. 2018; Sanders et al. 2016a). In GCEA, we capture both of these broader elements, but distinguish between the productivity costs experienced by patients and caregivers through our separate *productivity* and *family and caregiver spillover* components, where the former only refers to

Table 2: Mapping GCEA value petals to ISPOR value flower and second panel on cost effectiveness in health and medicine.

Category	GCEA	ISPOR	Second panel
Uncertainty	Outcome certainty	Value of hope	–
		Reduction in uncertainty	–
	Disease risk reduction	Insurance value	–
	Value of knowing	–	–
Dynamics	Dynamic net health system costs	Net costs	Medical costs paid for by patients out-of-pocket
			Medical costs paid for by third-party payers
			Future related medical costs (payers and patients)
			Future unrelated medical costs (payers and patients)
	Dynamic prevalence	–	–
	Societal discount rate	–	–
	Option value	Real option value	–
	Scientific spillovers	Scientific spillovers	–
Beneficiary	Patient-centered health improvements	Quality-adjusted life years (QALYs) gained	Longevity effects
			Health-related quality-of-life effects
			Other health effects (e.g., adverse events)
		Severity of disease	–
	Equity	Equity	–
	Family and caregiver spillovers	Productivity	Unpaid caregiver-time costs
			Cost of uncompensated household production
Additional value elements	Community spillovers	Fear of contagion	Important effects on sectors of the economy outside of healthcare
			Impact of intervention on educational achievement of population
			Production of toxic waste pollution by intervention
			Number of crimes related to intervention
			Cost of crimes related to intervention
	Productivity	Productivity	Cost of unpaid lost productivity due to illness
			Labor market earning lost (from worker absenteeism and presenteeism)

Table 2: (continued)

Category	GCEA	ISPOR	Second panel
	Adherence	Adherence improving factors	–
	Direct non-medical costs	Net costs	Patient-time costs Transportation costs Future consumption unrelated to health Cost of social services as part of intervention Cost of intervention on home improvements

productivity impacts on the patient and the latter concerns costs, utility impacts and productivity impacts to caregivers. Both the Second Panel and ISPOR value flower (through its "Net Costs" petal) recommend considering a wide range of costs, some of which appear within the GCEA as part of the *dynamic net health system costs* and *direct non-medical costs* petals.

Beyond what is provided in the Second Panel, GCEA also incorporates all novel value components that are part of the ISPOR value flower. More specifically, GCEA accounts for insurance value as part of the *disease risk reduction* component and combines ISPOR's value of hope and reduction in uncertainty into the single *outcome certainty* value element. These new terms are used to better distinguish between both of these value components and because these components can now be fit into the broader generalized and risk-adjusted cost effectiveness (GRACE) methodology; within GRACE, disease risk reduction considers the *ex ante* health risks a healthy individual experiences whereas outcome certainty considers the variability on future health outcomes when already having the disease.

Lastly, GCEA makes further modifications and additions beyond the ISPOR value flower. Unlike the ISPOR value flower, while GCEA does not include distinct petals for QALY gains and disease severity, GCEA accounts for both elements in its *patient-centered health improvements* component. However, this petal recommends using generalized risk-adjusted QALYs (GRA-QALYs) rather than conventional QALYs or other alternatives of QALYs such as equal value life-years gained (evLYG). Moreover, GCEA introduced novel petals, including a *societal discount rate*, *dynamic disease prevalence*, and the *value of knowing*.

While in theory, all petals should be estimated for all intervention, in practice the feasibility of estimating the petals and their impact on overall treatment value estimates may vary depending on the application. In practice, there will be multiple 'versions' of the GCEA value flower and value assessments will likely fall somewhere between conventional CEA (i.e. just the stem or pistil), GCEA with only readily estimable

petals included, and full GCEA (Figure 2). A treatment's indication, treatment modality, and data available to researchers likely will influence the degree to which GCEA petals are included in any value assessment. The Second Panel on Cost Effectiveness in Health and Medicine noted, "cost-effectiveness analysis is not by itself a sufficient decision-making standard and that it does not capture all relevant concerns"(Sanders et al. 2016b); while GCEA moves us towards a more comprehensive view of value, researchers should still consider issues surrounding data accuracy, value comprehensiveness, and other limitations when conducting real-world decision-making.

Standard patient-derived QALYs and direct healthcare costs are accounted for in the center of the flower and therefore do not themselves have petals.

3 Uncertainty

Although economists typically assume that individuals care about risk, and hence an outcome's uncertainty, health technology assessment bodies largely assume all individuals are risk neutral and ignore a technology's degree of uncertainty (Lakdawalla and Phelps 2020; Lakdawalla et al. 2018; Landeiro et al. 2020a). Hence, conventional CEA does not take into account outcome uncertainty either prior to or after an individual develops disease. By incorporating patient risk preferences, the Generalized and Risk Adjusted Cost Effectiveness (GRACE) method accounts for the value that patients accrue from reduced risk (variance of an outcome distribution) and tail-of-the-curve outcomes (skewness). Moreover, GRACE accounts for value accruing to individuals who have not developed the disease, but who are at risk by taking into account the fact that treatments can reduce or eliminate negative impacts that can contribute to future risk. The GRACE framework accounts for increases in outcome certainty through the incorporation of risk preferences in the generalized risk-adjusted quality adjusted life year (GRA-QALY).

The GRACE framework also accounts for disease severity. Empirical evidence indicates that patients with poorer health due to severe disease value the health gains from treatment more than comparable patients with a better health (e.g. a less severe disease) (Bobinac et al. 2012; Nielsen, Gyrd-Hansen, and Kjær 2021). This higher willingness to pay manifests in societal preferences and in public policies targeting treatments for severe diseases. For example, the Orphan Drug Act in the US granted an extended exclusivity period for severe disease treatments, hence recognizing their greater value (Gammie, Lu, and Babar 2015; Herder 2017; Legislatures 2023). The UK established the Cancer Drugs Fund to reduce delays and improve access to cancer treatments (Aggarwal et al. 2017). How GRACE incorporates disease severity into its value assessment framework is described in detail in Section 3.4.2. Also, we discuss how the alternatives to QALY as measures of patient-centered health improvement account for disease severity and compare them with GRACE in Section 4.1.

Diagnostic technologies confer a "value of knowing" by reducing uncertainty. Conventional CEA does not recognize this benefit and instead accounts only for the impact of improved diagnostics on treatment and its attendant impact on clinical outcomes. Stated preference methods have measured patient willingness to pay to better know their prognosis, presumably in part because this knowledge can help them and their families make more informed life choices (Phillips et al. 2006). Stated preference surveys indicate this benefit is distinct from the attendant clinical benefits of improved diagnostics and hence that value assessments should incorporate this component of value separately (Lakdawalla et al. 2018).

The following section further describes outcome certainty, disease risk reduction, and the value of knowing. It also describes an empirical application and a methods overview for implementing the GRACE framework.

3.1 Outcome Certainty

As pointed out in the ISPOR Value Flower, risk aversion and prudence of patients play a significant role in decision making process of treatment choice(Lakdawalla et al. 2018). Therefore, the value patients place on treatments depends on their health outcome distribution and not just on mean values.

Risk-averse patients value treatments that reduce the variance of their future health (Lakdawalla and Phelps 2021). A survey of cancer patients seeking a second opinion at diagnosis identified risk in treatment outcomes and prognosis as a source of disutility (Hillen et al. 2017). Previous research on the underlying microeconomic theory of healthcare valuation demonstrates that smaller risk is a non-trivial component of treatment value to patients (Lakdawalla and Phelps 2022, 2021). To aid in understanding, consider two treatments for glaucoma: a standard pair of eyeglasses and a new surgical intervention. Assume eyeglasses improve every patient's vision by 10 % (i.e. with certainty). The surgery, however, confers perfect vision to many patients but leaves some patients blind. Assume that, on average across all patients, surgery improves vision by 10 % despite the discrete outcome space. Conventional CEA would value these treatments equally because the average health improvement is 10 % for both, hence implying that patients are indifferent between the two options regardless of the differences in risk. However, a risk-averse patient may prefer the certain vision improvement offered by glasses to the range of possible outcomes attending surgery.

Rather than comparing average outcomes across treatments, a more complete analysis considering uncertainty in outcomes would compare certainty equivalents across treatments. A certainty equivalent is the guaranteed health benefit that a risk-averse or risk-loving consumer regards as equally preferable to a treatment's distribution of potential benefits. A simple monetary gambling example is included in the appendix to illustrate this distinction (Appendix Conceptual Example: Outcome Certainty).

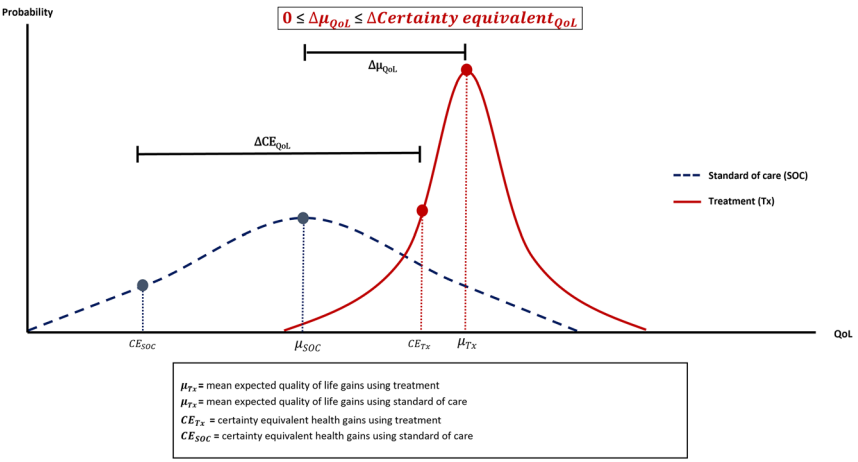

Figure 3: Conceptual representation of outcome certainty and certainty equivalence.

Figure 3 illustrates the difference between a certainty equivalent and an average health benefit. The blue and red curves represent the probability density functions for the health outcomes (measured by QoL) of the standard of care (SoC) and a treatment, respectively. Compared to SoC, the treatment has a greater average health benefit. Not only is the red treatment superior on average, but its variance is smaller (the red distribution is narrower than the blue distribution). Because of the reduced variance, the incremental certainty equivalent (ΔCE_{QoL}) exceeds the incremental average quality-of-life gain ($\Delta\mu_{QoL}$), as patients benefit not only from the treatment's increased average QoL but also from reduced risk (reduced variance).

When considering treatments for severe, often terminal, illness with poor quality of life in the sick state, patients may place additional value on treatments that offer highly favorable, "tail of the curve" health outcomes. In the same example of the two glaucoma treatments, for a patient who has almost lost their sight, even if they are risk averse, they may be willing to try the surgery to get perfect vision rather than improving their vision 10 % from the current poor vision. A survey of patients with metastatic melanoma and metastatic breast cancer found that 77 % of patients preferred treatments with a possibility of highly favorable outcomes, with some patients willing to pay over $90,000 for such a treatment, despite the average health benefit being no better than the standard of care(Lakdawalla et al. 2012). A survey of patients with non-small cell lung cancer found that patients were willing to exchange a year or more of mean survival in exchange for the chance of durable, tail-of-the curve

survival gains with both upside and downside survival risk(Shafrin et al. 2017). In Figure 3, if the treatment outcome distribution is right skewed, then ΔCE_{QoL} increases.

One key methodological advance for incorporating outcome certainty is GRACE's ability to calculate the value of health gains while incorporating both preferences for reduced variance and increased positive skewness in the distribution of health outcomes through generalized risk-adjusted quality-adjusted life years (GRA-QALY). Rather than directly comparing the average health gains, GRA-QALYs instead reflect certainty equivalents (Lakdawalla and Phelps 2021, 2022). For a risk neutral patient, the GRA-QALY and the QALY are equivalent, as they seek to maximize the expected value of their future health due to treatment. However, for a risk-averse patient as an example, the gains in GRA-QALY can be more than those in conventional QALYs. Section 3.4.1 illustrates calculation of the GRA-QALY.

3.2 Disease Risk Reduction

Whereas conventional CEA focuses only on a health technology's benefit to patients, individuals who do not currently have a given disease benefit from medical innovations that reduce their downside risk in the case that they are diagnosed with the disease in the future. The conventional CEA framework typically assesses the economic value of treatment from the perspective of the patients as the monetized health benefits net of treatment costs. However, the conventional framework overlooks the value of the treatment to the individuals who are not yet diagnosed with, but at risk of, the disease. These values include i) better expected health outcomes in the future and ii) reduced risk of the future health outcomes. The former value is represented by the expectation of the net treatment value of risk-neutral individuals. In addition, risk-averse individuals consider another value (the latter one) generated by the reduction in a utility loss from the uncertainty of having the disease, which is proportional to the net treatment value.

Specifically, for healthy risk-averse individuals, getting a disease or not in the future is a perceived risk and thus its impact on current utility is positively associated with how much their future quality of life could be negatively impacted by the disease. An introduction of a new treatment does not reduce the risk of contracting the disease itself but rather offers societal value by alleviating the loss of the quality of life incurred by the disease. Indeed, survey based methods have revealed that this risk reduction provides patients and non-patients alike with substantial value (McQueen et al. 2024). The *ex ante* value of the healthcare technology obtained by healthy individuals are referred to as insurance value(Lakdawalla et al. 2017). Just as in Section 2.1, quality of life is substituted with the certainty equivalent quality of life in the GRACE framework due to the convexity of the utility function of risk-averse individuals. Figure 4 provides a

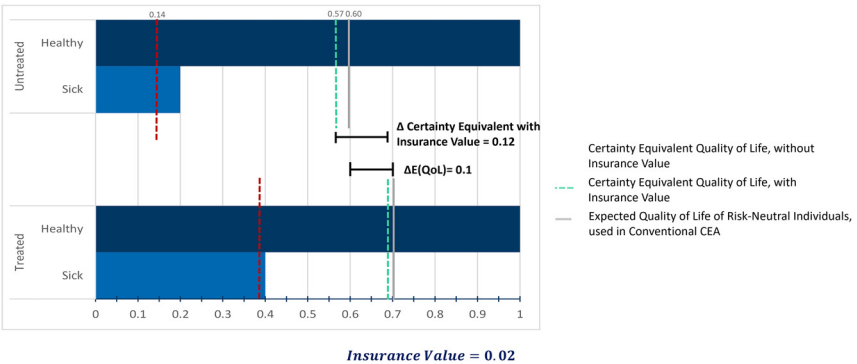

Figure 4: Conceptual representation of disease risk reduction.

conceptual example of how healthy, risk-averse members of the general population derive insurance value from a novel medical innovation using certainty equivalent quality of life. A more detailed example is available in Appendix Conceptual Example: Disease Risk Reduction.

To perceive an intervention's insurance value, it's important to frame what risk it averts. When a person with allergies pays for an epinephrine autoinjector, deriving comfort from carrying it around and experiencing anxiety whenever they forget to bring it with them to a restaurant, they are clearly appreciating the insurance value of that technology protecting them from anaphylaxis. People with food allergies have also reported a preference for a non-injectable form of epinephrine because the prospective of having to self-inject can be a source of anxiety and reason for hesitating to administer a dose (Shaker et al. 2023). So the epinephrine provides insurance value against anaphylaxis whereas the non-injectable formulation provides insurance value against needle phobia.

Indeed, studies eliciting willingness to pay for generous insurance coverage for an innovative treatment among samples of the healthy[2] general population show that, across indications, a substantial percentage of treatment value is captured by the disease-free population. In a stated-preference survey of willingness to pay for coverage of treatments for lung cancer, 89.8 % of the treatment value was accrued by individuals without lung cancer, who value improved survival if they are diagnosed with lung cancer in the future (Shafrin et al. 2021). Another stated preference survey of the healthy general population found that members of the general population were willing to pay $1,004 per year (compared to conventional CEA projections of

2 In the context of insurance value, the term "healthy" refers to individuals who are not diagnosed with the disease of interest.

$45.30 per year) for gene therapies in Duchenne muscular dystrophy (Shafrin et al. 2023). In a stated preference survey of three interventions for multiple sclerosis (MS), one third of the total value of the treatments was accrued to those without an MS diagnosis (Liu, Shim, and Lakdawalla 2016).

To incorporate the value from disease risk reduction into the value assessment, GCEA recommends estimating GRA-QALY and RASA-WTP under the GRACE framework. Unlike stated preference surveys that have frequently been used to estimate this value component, the GRACE framework is easily generalizable to a variety of disease and treatment combinations because no matter what the disease of interest is, once patients risk preference over quality-of-life metric and the loss of quality of life by the disease are given, GRACE can always account for the value from disease risk reduction.

3.3 Value of Knowing

Diagnostic tests provide value to patients, practitioners, and caregivers as improved knowledge can lead to better decision making. These better treatment decisions result in changes to patient health outcomes (e.g. QALYs) and cost. Consider a lung cancer patient who uses an improved diagnostic test to identify whether they have anaplastic lymphoma kinase (ALK) gene-positive tumors. Based upon this knowledge, patients can access targeted therapies, such as alectinib, which has improved median overall survival for ALK-positive patients compared to traditional chemotherapy (Jiang et al. 2022). Costs may also change; costs may increase if perhaps alectinib is more expensive than traditional chemotherapy, but may also fall if use of more targeted treatment leads to reduced hospitalizations and medical costs. The ability of diagnostics tests to impact health outcomes and costs through better decision making is already captured by conventional CEA.

However, patients may also derive value from new diagnostics simply from having more knowledge about their health even if the outcome of the diagnostic test does not change decision-making. This “value of knowing” is not included in conventional CEA. Suppose that a patient is diagnosed with Huntington’s disease. Since there is currently no treatment, the diagnostic enables no direct health benefit within the conventional CEA framework. However, patients may be able to take additional vacations, spend more time with family, or save money to cover the more intensive care required as the disease progresses. These choices might improve patient QoL compared to not knowing they had the disease. In addition to the planning value enabled outside of a healthcare context, studies have demonstrated that there is value in “knowing for knowing’s sake” to patients who have undiagnosed symptoms (Asch et al. 1990). More broadly, stated preference surveys have

determined that many patients derive planning value from diagnostics, whereby they can make utility-maximizing financial, work, reproduction, retirement, and end-of-life care plans (Lee et al. 2010; Neumann et al. 2001). Current research has examined the value of knowing as it is accrued to family members, and family members have reported deterioration of their own health and quality of life as a result of limited information in cancer diagnosis (Lavallée et al. 2019).

The "value of knowing" need not always be beneficial to patients. For example, consider the case where a patient is diagnosed with amyotrophic lateral sclerosis (ALS). ALS results in progressive, full body paralysis and early death with no cure available. Simply knowing that their future health may inevitably be poor can cause distress, fear, and disutility for patients, even while their current health is quite similar to that of a healthy member of the general population. This "negative" value of knowing is evidenced by the existence of genetic counselors and the prescription of behavioral therapy for many patients of severe disease (Dugan et al. 2003; Kim et al. 2021; González-Martín et al. 2023).

To estimate the value of knowing, stated preference methods can be utilized to determine the willingness to pay to gain the psychological benefit and increased certainty for making future plans. These preference surveys follow both conventional and behavioral economic theory that patients are willing to pay for a diagnostic(Kahneman 1979; Lee et al. 2010). Two forms of stated preference survey can be utilized to elicit the value of knowing from patients. Contingent valuation methods describe a hypothetical screening to patients and ask individuals how much they would be willing to pay to have access to that screening (Phillips et al. 2006). Conjoint analysis requires participants to compare hypothetical scenarios by ranking, rating, or selecting scenarios after evaluating them across a collection of attributes (Phillips et al. 2006). The value of knowing would be any difference between the willingness to pay for the diagnostic test and the *ex ante* direct health benefit to the patient enabled by the improved diagnostic. For example, if a patient is willing to pay $75,000 for a diagnostic that enables a 0.5 QALY gain from better treatment selection, then using standard WTP for a QALY the value of knowing is $75,000 – (0.5QALYs)*($100,000/QALY) = $25,000. One could then readily incorporate this value into GCEA.

3.4 Empirical Application #1: Using GRACE to Estimate Treatment Uncertainty & Disease Risk Reduction

GRACE incorporates the value of treatment uncertainty and disease risk reduction into a single unifying framework. GRACE accomplishes this through three key steps: addressing the change in generalized risk-adjusted QALYs (GRA-QALY), measuring the risk- and severity-adjusted willingness to pay (RASA-WTP), and deriving value

Box 1: Overview of GRACE implementation.

1. **Calculate generalized-risk adjusted quality-adjusted life years (GRA-QALY)**
   a. Compute the distribution of health outcomes
   b. Derive the risk-adjusted QoL gains using the certainty-equivalent (CE) gain in QoL
   c. Derive the risk-adjusted longevity gains using the adjusted QoL (marginal rate of substitution between survival and QoL)
   d. Compute GRA-QALY gains by summing the risk-adjusted QoL longevity gains
2. **Calculate risk-aversion and severity-adjusted willingness to pay (RASA-WTP)**
   a. To get the RASA-WTP, adjust the WTP of the traditional CEA using the risk-aversion and severity-adjustment factor
   b. To account for disability in the baseline period, apply the permanent disability factor to RASA-WTP
3. **Value metrics. Calculate risk-aversion and severity-adjusted net monetary benefit (RASA-NMB)**

metrics for GRACE such as an ICER or risk- and severity-adjusted net monetary benefit (RASA-NMB) (Box 1). A description of each phase follows in the section below. For a full derivation of how to use GRACE to calculate RASA-NMB and ICER under GRACE see Lakdawalla and Phelps (*Journal of Benefit-Cost Analysis* 2023) study.[3]

3.4.1 Generalized Risk-Adjusted Quality-Adjusted Life-Year (GRA-QALY)

The GRA-QALY is calculated in four overarching steps (Lakdawalla and Phelps 2022). First, compute the distribution of health outcomes in both the treatment and comparator groups for each study period just as in the conventional CEA model.

3 A more detailed derivation from the Lakdawalla Phelps Journal of Benefit-Cost Analysis (2023) paper is as follows:

$$NMB_{GRACE} = \phi \sum_{j=0}^{\infty} \beta^j \left\{ \mu_{pj} \left[K \frac{[EW(H_{sj} + B_j)]}{W(H_0(1-d^*))} H_0 - Cost_j^T \right] + p_j^U \left[K \frac{[EW_j(T)]}{W(H_0(1-d^*))} H_0 - \Delta Cost_j \right] \right\}.$$

ICER calculation:

$$K \frac{W'(E(H_{si}))}{W(H_0(1-d^*))} H_0 > \frac{\sum_{j=0}^{\infty} \beta^j \left[\mu_{pj} Cost_j^T + p_j^U \Delta Cost_j \right]}{\sum_{j=0}^{\infty} \beta^j \left\{ \frac{W(H_0(1-d^*))}{W'(E(H_{si}))} \left[\mu_{pj} \frac{[EW(H_{sj}+B_j)]}{W(H_0(1-d^*))} + p_j^U \frac{[EW(H_{sj}+B_j) - EW(H_{sj})]}{W(H_0(1-d^*))} \right] \right\}}$$

it.

One of the most widely used CEA methodologies is a Markov model with clinical inputs from clinical trials and/or epidemiological statistical data. Consider a simple three-year model with four health states: sick, pre-treated patients (QoL = 0.40), small health improvements (QoL = 0.50), large health improvements (QoL = 0.80) and death (QoL = 0) as shown in Table 3. Assume that there are two interventions being compared in a value assessment: SoC and a new innovative drug. All patients with the disease are sick at baseline (i.e. QoL = 0.40 in year 0). If a patient receives SoC, she will have QoL of 0.50 for sure in year 1 but die in year 2. The QoL of a patient who receives the new treatment can be 0.40 or 0.80 with probabilities of 50 % and 50 % in year 1. In year 2, she will have an 80 % chance of dying and a 20 % of surviving with QoL of 0.40.

The QALY gains (ΔQALY) in the conventional CEA are composed of the gains from the improved expected QoL (ΔQoL) holding survival constant (LY_{SoC}) (QoL gains) and the gains from additional life-years (LYs) (ΔLY) weighted by the expected QoL ($QoL_{Treatment}$) (longevity gains) (Equation (1)).

$$\Delta QALY\left(= \Delta QoL \times LY_{SoC}\right) + \left(QoL_{Treatment} \times \Delta LY\right) \quad (1)$$

Given no patients die in year one for both the SoC or treatment groups but all patients in the SoC group die in year 2, QoL gains between the two groups only exist in year one and longevity gains are experienced only in year 2. Accordingly, QoL gains in this example are expressed as the following:

$$\Delta QoL \times LY_{SoC} = \{(0.40 \times 50\% + 0.80 \times 50\%) - (0.50 \times 100\%)\} \times 100\% = 0.10$$

Moreover, given none of the patients in the SoC group survives in year two but 20 % of the treatment group survives that year, the additional life-years (ΔLY) relative to the SoC group are equal to 0.20 and longevity gains are expressed as:

Table 3: Distribution of health outcomes.

Intervention	Health state	Quality of life (QoL)	Year		
			0	1	2
SoC	Dead	0.00			100 %
	Sick	0.40	100 %		
	Small improvement	0.50		100 %	
	Large improvement	0.80			
New treatment	Dead	0.00			80 %
	Sick	0.40	100 %	50 %	20 %
	Small improvement	0.50			
	Large improvement	0.80		50 %	

Table 4: Comparison between QALY gains of CEA and GRA–QALY gains of GRACE.

(GRA-)QALY decomposition	CEA	GRACE
Quality-of-life improvement (ΔQoL or $\Delta E[U(H)]$) of treatment group in year 1	0.10	0.11
Life years for SoC group (LY_{SoC})	1	1
Additional LY or survival of treatment group (ΔLY)	0.20	0.20
Quality of life of treatment group ($QoL_{Treatment}$ or $E[U(H_{Treatment})]$) in year 2	0.40	0.30
(GRA-)QALY gains (ΔQALY or ΔGRA_QALY)	**0.18**	**0.17**

Bold values here indicate the final outcomes of GRA-QALY and QALY estimations and distinguish these from the other values in table.

$$\mathrm{QoL}_{\mathrm{Treatment}} \times \Delta\mathrm{LY} = 0.40 \times 20\% = 0.08$$

As a result, the incremental QALY gain under CEA is as follows (also summarized in Table 4):

$$\Delta\mathrm{QALY} = \left(\Delta\mathrm{QoL} \times \mathrm{LY}_{\mathrm{SoC}}\right) + \left(\mathrm{QoL}_{\mathrm{Treatment}} \times \Delta\mathrm{LY}\right) = 0.10 + 0.08 = 0.18$$

The GRA-QALY gain of GRACE (ΔGRA_QALY) has the same structure as the CEA's QALY gain but there are at least two differences that diverge from the properties of the QALY (Equation (2)). First, GRACE explicitly accounts for uncertainty in quality-of-life improvements, computing the expected value of changes in and levels of utility from health-related quality of life. Second, GRACE accounts for consumer risk preferences over quality-of-life, by explicitly modeling the utility function over health-related quality of life. This results in the following adjusted equation.

$$\begin{aligned}\Delta\mathrm{GRA\_QALY} &= \Delta\mathrm{QoL}_{\mathrm{CE}}{*}\mathrm{LY}_{\mathrm{SoC}} + \mathrm{QoL}^{\mathrm{Adj}}_{\mathrm{Treatment}}{*}\,\Delta\mathrm{LY}\;\Delta\mathrm{GRA\_QALY} \\ &= \left(\Delta\mathrm{E}[\mathrm{U}(\mathrm{H})]\mathrm{Qo}\Delta\mathrm{QoL}_{\mathrm{CE}} \times {*}\mathrm{LY}_{\mathrm{SoC}}\right) \\ &\quad + \left(E[U(H_{\mathrm{Treatment}})]\mathrm{QoL}^{\mathrm{Adj}}_{\mathrm{Treatment}}\mathrm{QoL}^{\mathrm{Adj}}_{\mathrm{Treatment}} \times {*}\,\Delta\mathrm{LY}\right) \qquad (2)\end{aligned}$$

$$\text{where } \Delta E[U(H)] \equiv E[U(H_{\mathrm{Treatment}}) - U(H_{\mathrm{SoC}})]$$

For the QoL gains, utility gains of the treatment group holding survival the same as the SoC group presented as $\Delta E[U(H)]{*}\mathrm{LY}_{\mathrm{SoC}}$ in Equation (2), GRACE replaces the traditional quality of life weight with the expected utility from health-related quality of life. To calculate expected utility, the analyst needs the distribution of health, H, along with an appropriate health-related utility function. Ideally, health should be measured in a visual analogue scale, but in practice, this is likely to be numerically similar to measures of traditional quality of life (QoL) weights; for simplicity, therefore, we use traditional QoL weights as inputs in our example. In this example, we employ an expo-power utility function with preference parameters elicited from a nationally representative US population by prior research, $U(H) = 1 - e^{-2.62H^{2.18}}$ (Mulligan et al. 2024b).

In year 1, SoC patients experience QoL of 0.50, while treatment patients face a 50/50 chance of QoL equal to 0.40 or 0.80. Thus, expected utility for the SoC and treatment patients in this period is:

$$\mathrm{EU}(H_{\mathrm{SoC}}) = \left(1 - e^{-2.62(0.5)^{2.18}}\right) \times 100\,\% = 0.44$$

$$\mathrm{EU}(H_{\mathrm{Treatment}}) = \left(1 - e^{-2.62(0.4)^{2.18}}\right) \times 50\,\% + \left(1 - e^{-2.62(0.8)^{2.18}}\right) \times 50\,\% = 0.55$$

Therefore, the QoL gain in period one is given by:

$$\begin{aligned}\Delta E[U(H)] \times \mathrm{LY}_{\mathrm{SoC}} &= (\mathrm{EU}(H_{\mathrm{Treatment}}) - \mathrm{EU}(H_{\mathrm{SoC}})) \times \mathrm{LY}_{\mathrm{SoC}} = (0.55 - 0.44) \times 100\,\% \\ &= 0.11\end{aligned}$$

For the longevity gains, utility gains during additional LYs of the treatment group are presented as $E[U(H_{\mathrm{Treatment}})] \times \Delta LY$ in Equation (2). Since all SoC patients die and 20 % of treatment patients are expected to experience utility of 0.30 ($= 1 - e^{-2.62(0.4)^{2.18}}$) in year 2, the longevity gain is:

$$E[U(H_{\mathrm{Treatment}})] \times \Delta\mathrm{LY} = 0.30 \times 20\,\% = 0.06$$

At this point, the GRACE calculation becomes quite similar to traditional cost-effectiveness, simply substituting $EU(H_{\mathrm{Treatment}})$ for $\mathrm{QoL}_{\mathrm{Treatment}}$ and substituting $EU(H_{\mathrm{Treatment}}) - EU(H_{\mathrm{SoC}})$ for ΔQoL. The resulted GRA–QALY gains are:

$$\begin{aligned}\Delta\mathrm{GRA}_{\mathrm{QALY}} &= \left(\Delta E[U(H)]\mathrm{Qo}\Delta\mathrm{QoL}_{\mathrm{CE}} \times {}^{*}\mathrm{LY}_{\mathrm{SoC}}\right) \\ &\quad + \left(E[U(H_{\mathrm{Treatment}})]\mathrm{QoL}^{\mathrm{Adj}}_{\mathrm{Treatment}}\mathrm{QoL}^{\mathrm{Adj}}_{\mathrm{Treatment}} \times {}^{*}\Delta\mathrm{LY}\right) \\ &= 0.11 + 0.06 = 0.17\end{aligned}$$

These results are summarized in Table 4.

3.4.2 Risk-Aversion and Severity-Adjusted Willingness to Pay (RASA-WTP)

RASA-WTP adjusts for disease severity[4] and for pre-existing disability. If there are diminishing marginal returns to health improvement, the marginal value of health improvement will be higher for people in sicker states. Thus, more severe disease implies higher willingness to pay for health improvement. Meanwhile, pre-existing disability limits consumption opportunities. For instance, mobility limitations make it harder to travel or enjoy certain kinds of recreational activities. GRACE accounts for the way pre-existing disability further increases the willingness to pay for

4 More discussions on disease severity in value assessment are included in Patient-Centered Health Improvements.

health improvement, because the opportunity costs of giving up consumption fall (Lakdawalla and Phelps 2022). Defining K as the traditional willingness to pay for a QALY, the GRACE RASA-WTP is given by:

$$\text{RASA - WTP} = K\lambda D$$

Here, λ is the disease severity adjustment factor, and D is the disability adjustment factor. The disease severity adjustment factor satisfies $\lambda = \frac{W'(\mu_H)}{W(1)}$. Here, μ_H is the expected QoL for patients on SoC in the first period of the model, and the denominator of this ratio represents utility from perfect health. In principle, this adjustment factor can be calculated for any period, but by convention, we select the first period here. In our example, $\mu_H = 0.5$. Moreover, the utility function shown above possesses the first derivative, $W'(\mu_H) = ((2.18)(2.62)\mu_H^{(2.18-1)}) \bullet \exp(-2.62\mu_H^{2.18})$. Therefore, the disease severity adjustment factor is given by:

$$\lambda = \frac{\left((2.18)(2.62)(0.5)^{(2.18-1)}\right) \bullet e^{-2.62(0.5)^{2.18}}}{1 - e^{-2.62}} = 1.52$$

Finally, the disability adjustment factor is given by $D \equiv \frac{W(1)}{W(H_{0d})}$, where H_{0d} represents quality-of-life before the onset of illness but including any pre-existing disability. In the US, it is conventional to assume that average quality-of-life in the general population is approximately 0.825 (Janssen et al. 2019). Therefore, the disability adjustment factor is given by:

$$D = \frac{1 - e^{-2.62}}{1 - e^{-2.62(0.825)^{2.18}}} = 1.13$$

As a result, when the conventional WTP is assumed to be \$100,000, RASA-WTP without and with considering the permanent disability is \$152,339 (=1.52*\$100,000) and \$171,967 (=1.52*1.13*\$100,000), respectively.

3.4.3 Risk-Aversion and Severity-Adjusted Net Monetary Benefit (RASA-NMB)

The health economic value assessed by the GRACE framework is summarized by RASA-NMB. Just as NMB in conventional CEA, RASA-NMB is calculated as the monetized health benefit gains net of the additional opportunity costs of the resource used. The key difference is that GRACE uses GRA-QALY gains and RASA-WTP instead of QALY gains and WTP/QALY, respectively. For simplicity we assume there are no differences in cost between SoC and the new treatment. In this case, NMB of the conventional CEA is \$18,000 (=0.18*\$100,000) and RASA-NMB of GRACE without and with considering the permanent disability is \$25,947 (=0.17*\$152,339) and \$29,291 (=0.17*\$171,967), respectively. Positive values of NMB indicate the health

benefits are more than the cost; negative values indicate health benefits are less than the costs.

4 Dynamics

Conventional CEAs largely assume that prices and treatment dynamics do not change over time. While predicting the future is never easy, there are at least five different ways in which these healthcare market dynamics could be better incorporated into value assessments. First, pharmaceutical prices change drastically over their life cycles due to generic entry after brand-name drugs lose their market exclusivity ("dynamic net health system cost"). Second, disease prevalence can become more or less common over time, which may make the full societal impact of a treatment more or less valuable depending on the sizes of affected populations in the future ("dynamic disease prevalence"). Third, health improvement for current patients may be more beneficial if these health improvements allow patients to survive, maintain, or improve their health until superior health technologies arrive in the future ("option value"). Fourth, treatment innovations – both successes and failure – can create "scientific spillover," providing valuable scientific and market information to other firms, which can expedite the development of future innovation. Finally, treatment benefits and costs may accrue differently over time, which requires adjustment to the discount rates used in value assessments to ensure neither element is overvalued nor undervalued ("societal discount rate"). In this section, we provide recommendations on how researchers can incorporate these five value components into existing CEA.

4.1 Dynamic Net Health System Cost

While most conventional CEAs assume a drug's market launch price is constant over time (Whittington et al. 2023), in practice prices never remain constant. Drug prices are dynamic and change over their life cycle; prices may increase prior to the drug's loss-of-exclusivity (LOE) and later decrease due to competition, especially post-LOE from genericization or biosimilar entry (Bhattacharya and Vogt 2003; Conti and Berndt 2016; Goldman et al. 2018). For example, prices for enalapril, fluoxetine and ranitidine in the Netherlands fell by 61 %, 51 % and 69 %, respectively, after the introduction of the first generic drug (Boersma et al. 2005; Vondeling et al. 2018). Other analyses indicate that for drugs in the US that lost exclusivity and experienced generic entry between 2002 and 2014, average price decreased by 51 % in the first year and 57 % after the second year (Aitken 2016). In

specific markets such as oral cancer therapies, prices fell by 60–90 % within 12 months of LOE (Padula et al. 2016). Moreover, more substantial price reductions have been reported with increased generic entry over time, such as the 96 % price decrease of imatinib relative to its brand-name counterpart (Campbell et al. 2019).

To better incorporate pricing dynamics, we recommend the incorporation of dynamic net health system costs into the value assessment framework, but the manner in which pricing is incorporated may vary by type of technology (e.g. small molecule vs. biologic vs. cell and gene therapy) (McQueen et al. 2023). According to the FDA, price decreases after generic entry range from 54 % with two generic competitors to more than 95 % with six or more generic entrants (Conrad and Lutter 2019). Yet, when considering biologic drugs specifically, biosimilar entry often leads to smaller and more variable price decreases that depend on the biosimilars' eventual uptake; price decreases one-year after biosimilar entry can range from 2.4 % to 59.3 %, with the low end of the spectrum largely due to low biosimilar uptake (Hernandez et al. 2022). Furthermore, the timing of genericization depends on the type of health technology. Previous estimates indicate that generally drugs in the US do not experience genericization for nearly 13 years after initial launch and, for more innovative drugs, this exclusivity period rises to around 14 years (Kesselheim et al. 2017); in Europe, this exclusivity period is estimated to be at 11 years and may be subject to change following new legislation going forward (Miglierini 2022; "Reform of the EU pharmaceutical legislation" 2023). Moreover, certain drug types – such as gene therapy products or drugs that require a special device for administration – may never experience genericization due to their developmental complexity (Kolchinsky 2017). In the US, the recently passed Inflation Reduction Act (IRA) granted CMS the ability to lower prices of some drugs essentially by fiat, which provides yet another reason for dynamic modeling even if a drug is unlikely to face generic or biosimilar competitors (Arad and McClellan 2022; Whittington et al. 2023).

Implementing price reductions due to genericization can be done through two methodologies: (i) based on a proportional reduction from a branded drug's manufacturer price (e.g. wholesale acquisition cost, or WAC, in the US) or (ii) based on a multiplier applied to a health technology's marginal cost of production. While the former is more commonly used, previous percentage reduction estimates may fail to reflect important drug pricing trends. This is particularly relevant since the size of rebates in the US, or discounts elsewhere, has increased the gross to net pricing spread (Hernandez et al. 2020), applying different pricing reductions is necessary for different types of treatments, and (iii) prices may vary based on the disease for which the treatment is indicated.

Regarding the first point, researchers that wish to apply proportional reductions to simulate generic entry should do so based on net – rather than gross – prices, or should rely on more recent data on proportional price reductions. Consider the case where a drug was priced at $100 and after genericization fell to $5; this represents a 95 % discount. Nowadays, however, this same drug may have a wholesale acquisition cost of $200, but with a $100 rebate, for a net cost of $100. If one applied the 95 % discount to the gross price ($200), one would estimate the generic price to be $10 (i.e. $200 × (1–95 %)), which is double the actual generic price ($5). Thus, one should either apply the historical price discount (95 %) to the net price (i.e. $100), if available, or use more recent data which would indicate that prices fall by 97.5 % (i.e. $\frac{\$200-\$5}{\$200} = 97.5\,\%$).

Second, analysts should apply different price reductions from WAC for small molecules, biologics, and cell/gene therapies given price decreases due to genericization may be lower for biologic products since biosimilars are more difficult to manufacture (Makurvet 2021), to be approved by regulatory agencies, and there are limited data available on how prices have changed for cell and gene therapy products. Finally, price decreases as a percentage of WAC are likely larger for rare disease and precision drugs given they are often priced at higher multiples of their production cost than widely used drugs to generate a comparable return despite having fewer patients to treat (Makurvet 2021).

While less commonly used, estimating future drug costs after LOE as a multiple of a drug's marginal cost of production may be a more appropriate approach. This approach is more aligned to economic theory; in competitive markets – such as a generic drug market when a highly profitable drug goes off patent and when the barriers to entry are relatively low – prices fall towards these generic drugs' marginal costs of production in equilibrium due to competition between multiple generic manufacturers. However, the information needed to utilize this approach may be more difficult for researchers to access. First, the marginal costs of production are not well known outside of the drug manufacturer. However, researchers could estimate cost of goods sold (COGS) for the product of interest – or analog products if necessary – based on financial reports filed with financial bodies, such as the Securities and Exchange Commission (SEC) in the US.

Second, there is a lack of consensus in the literature about the appropriate multiplier to use to infer the equilibrium price based on COGS. The best study to date estimates that gross margins are approximately 50 % in the US, which implies that the prices of generic drugs are two times the COGS for generic drugs (Sood et al. 2017).

Finally, while this approach does align more closely to economic theory, in practice not all drugs experience considerable competition when losing market

exclusivity. Even then, given the tendency for policymakers to eventually target old drugs that remain expensive with policy like the IRA, a GCEA of a complex biologic could earn a dynamic pricing petal by exploring in a sensitivity analysis the impact of potential policy that lowered the drug's price closer to its estimated COGS so that it was clear how much of a novel drug's societal value hinged on it dropping in price in the future.

4.2 Dynamic Disease Prevalence

In addition to changes in drug prices over time, conventional CEA methods often exclude how the prevalence of the disease changes over time. This concept of dynamic disease prevalence – or "dynamic prevalence" for brevity – becomes non-trivial for some diseases when model horizons in CEA are sufficiently long. For example, consider the case of curative therapies such as recent advances for treating the hepatitis C virus. The disease's prevalence is projected to decrease over time such that a novel hepatitis C virus drug decades into the future will treat a smaller patient population and thus the cost of treatments to the system may fall dramatically in the long run (Razavi et al. 2014). In contrast, new treatments for Alzheimer's disease in the future may prove more costly to the health system given that the global prevalence of Alzheimer's disease – and thus the population in need of treatment – is estimated to triple to nearly 153 million by 2050 (Nichols et al. 2022). As an even more salient example, as the burden of drug-resistant infections to society is expected to climb over time, the value of new antibiotics that come to market today may rise in the future even if physicians are likely to prefer treating current patients with older antibiotics to maintain the novel antibiotics' potency in the future (Shafrin et al. 2022). Proposals to offer significant incentives for antibiotic development in the form of guaranteed subscriptions make sense if considering dynamic prevalence whereas conventional CEA would likely conclude that such high spending to treat the few patients who need these drugs today is not cost-effective (Bennet 2023; Glover et al. 2023).

Accordingly, to account for both dynamic net health system costs and dynamic prevalence over time, GCEA recommends the use of "stacked" cohorts that include impacts to current and future patients starting treatment. The stacked cohorts should include (i) the changes in prices due to competition and generic/biosimilar entry and (ii) the changes in prevalence over time. Patients who initiate therapies in the future may face lower total drug costs because the treatments are closer to genericization; also, there may be more or fewer patients who initiate treatment in the future due to dynamic prevalence. An example of how to apply the stacked cohort approach is described in Section 3.3.

4.3 Empirical Application #2: Stacked Cohort Approach for Incorporating Dynamic Net Health System Cost & Dynamic Prevalence

To demonstrate how to incorporate dynamic net health system costs and dynamic prevalence into GCEA, consider the following stylized example, where a hypothetical brand-name small molecule drug, Drug A, has just been approved by the FDA and has entered the market to treat a hypothetical chronic disease. Patients treated for the chronic disease need to take Drug A for 15 years and the annual WAC is $10,000 per person upon market entry; further, Drug A is predicted to always be available on the market. Our goal is to develop a CEA model with a lifetime model horizon of 70 years that incorporates the aforementioned pricing dynamics; for our example walk-through, we utilize a 40-year model horizon for simplicity but report results for both the simplified model and full 70-year model in Table 6.

Implementing pricing dynamics requires three key steps: incorporating (i) genericization (dynamic net health system costs), (ii) stacked cohorts, and (iii) dynamic prevalence (Box 2). In the first step, researchers will need to first identify the branded drug's exclusivity period and the timing of generic entry (Whittington et al. 2023). Following Drug A's classification as a small-molecule product, we assumed that the generic entry would begin 13 years post-approval in line with the IRA's proposed drug negotiation timeline and estimates provided by previous studies (Goldman et al. 2023; Kesselheim et al. 2017). Second, researchers should incorporate changes in annual drug prices pre- and post-genericization. We assumed that (i) real drug price remains constant prior to LOE and (ii) generic entry leads to a 51 % reduction in the first year after LOE and then falls by 95 % in all subsequent years (Aitken 2016; Conrad and Lutter 2019; Gupta et al. 2019). Finally, GCEA incorporates the annual uptake of the generic drug by patients (Whittington et al. 2023). For simplicity, our example assumes that there is a 100 % uptake of the generic molecule after LOE or else that the brand drug's net price drops close to that of generics (as one would expect payors to rationally negotiate, though recent biosimilar uptake and biologic pricing dynamics post-LOE are more variable) (Hernandez et al. 2022). When incorporating all these inputs for genericization, Drug A's annual cost (undiscounted) is $10,000 per year through year 13, decreases to $4,900 in year 14 and further falls to $500 for years 15 and beyond (Table 5). This approach incorporates genericization but in a static manner; future cohorts who use the treatment have not been taken into account.

To reflect the initiation of Drug A by future patients, new patient cohorts are introduced each year in our example until 10 new cohorts have been included and are "stacked" over the model horizon. While in practice we highly recommend using

Box 2: Overview of dynamic net health system costs and dynamic prevalence implementation.

1. **Genericization (dynamic net health system costs)**
   To incorporate drug price changes over time:
   a. Identify the branded drug's exclusivity period and timing of generic entry
   b. Identify the changes in drug price pre- and post-genericization
   c. Apply market share assumptions during treatment duration (annual generic uptake)
2. **Stacked cohorts**
   a. Introduce new patient cohorts each year in the model and "stack" them
   b. Each patient cohort will experience branded prices from treatment initiation until year of genericization, and generic prices for years post-genericization
3. **Dynamic prevalence**
   a. Determine the annual disease incidence for each year of the model as the size of each cohort
   b. Weight each cohort by their size. The sum of the weights is 1
   c. Take a weighted average of the drug costs across all cohorts for each year in the model. To calculate the total health system cost over the study period, sum all of the year-specific total costs across every year of the model (discount can be applied)

additional cohorts (e.g. 70 cohorts if the model extends 70 years since patients will forever benefit from the upgrade to outcomes that a novel drug offers, even if it's later displaced by better treatments), we selected 10 cohorts to simplify this empirical example. As shown in Table 5, this is implemented such that only one patient cohort (Patient Cohort 1) will take Drug A in the first year of the model, two patient cohorts (Patient Cohort 1 and Patient Cohort 2) will take the drug during year 2, three patient cohorts will take the drug in year 3, and so on. These added cohorts will experience the same decrease in Drug A's price upon generic entry, such that patient cohorts that would enter the model in year 14 or later will only experience the reduced post-genericization price throughout their entire treatment period (Figure 5 and Table 5).

To determine how the prevalence of a disease will change over time – and thus the expected size and weights of future patient cohorts – researchers must determine the annual incidence of the disease for each year of the model. The model will start with a patient population size based on current prevalence, but future incident patient populations will be added over time. Moreover, prevalence should be estimated specifically for the population intending to use the treatment. Our example assumes that the disease's annual incidence will steadily increase from 10 % during the first year to 12.0 % in 10 years (or 39.2 % in the 70-year model) (Table 5). The patient cohort weights are calculated as $\frac{W_c}{W}$, where W_c is the cohort size and $W = \sum_c W_c$ is the total size across all cohorts. Following this example, Patient Cohort 1 gets the least weight for having the smallest disease incidence (and thus cohort size)

Table 5: Demonstration of dynamic net health system costs and dynamic prevalence in GCEA (simplified example).[a]

Patient cohort	Annual chronic disease incidence	Patient cohort weight	Model years																	Total cohort costs
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	…	40	
1	10.0 %	9.13 %	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$4,900	$500	$ -	…	$ -	$135,400
2	10.2 %	9.32 %	$ -	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$4,900	$500	$500	…	$ -	$125,900
3	10.4 %	9.50 %	$ -	$ -	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$4,900	$500	$500	…	$ -	$116,400
4	10.6 %	9.69 %	$ -	$ -	$ -	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$4,900	$500	$500	…	$ -	$106,900
5	10.8 %	9.89 %	$ -	$ -	$ -	$ -	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$4,900	$500	$500	…	$ -	$97,400
6	11.0 %	10.08 %	$ -	$ -	$ -	$ -	$ -	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$4,900	$500	$500	…	$ -	$87,900
7	11.3 %	10.28 %	$ -	$ -	$ -	$ -	$ -	$ -	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$4,900	$500	$500	…	$ -	$78,400
8	11.5 %	10.49 %	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$10,000	$10,000	$10,000	$10,000	$10,000	$10,000	$4,900	$500	$500	…	$ -	$68,900
9	11.7 %	10.70 %	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$10,000	$10,000	$10,000	$10,000	$10,000	$4,900	$500	$500	…	$ -	$59,400
10	12.0 %	10.91 %	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$ -	$10,000	$10,000	$10,000	$10,000	$4,900	$500	$500	…	$ -	$49,900
…	…	…	…																		…

[a]While the modeled costs in this example are undiscounted, analysts should discount over time.

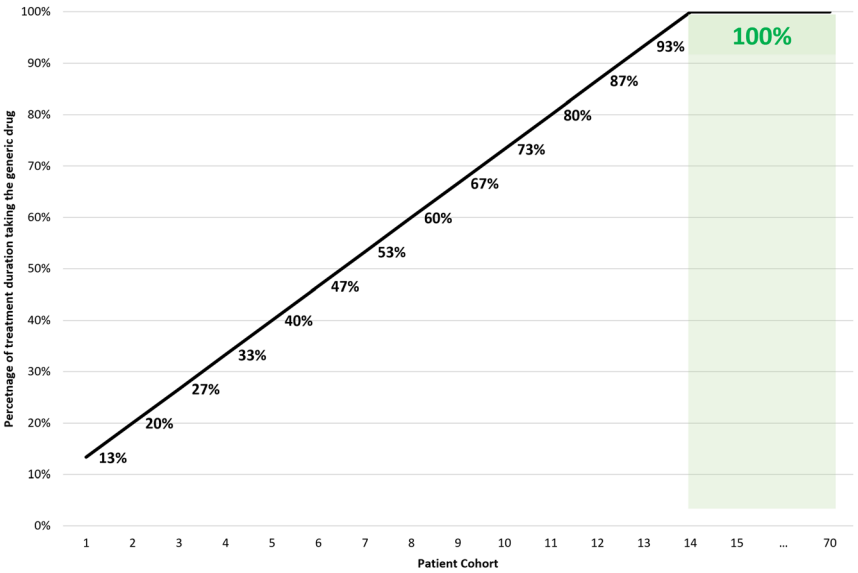

Figure 5: Percentage of treatment duration (15 years) that each patient cohort takes the generic drug in the 70-year model.

while Patient Cohort 10 (or Patient Cohort 70 in the longer model) receives the greatest weight in the analysis given it has the largest disease incidence.

With the incorporation of the above model inputs, we find that there is a significant change in the resulting, undiscounted average annual per patient treatment cost of Drug A; while the results were undiscounted here, researchers should discount drug costs over time. When using conventional CEA and ignoring any changes in price – such that Drug A's cost was fixed at $10,000 – per patient cost of Drug A over the model horizon was $150,000 (calculated as the sum of Drug A's costs over the 40-year model horizon for a single patient cohort) (Table 6). When only incorporating price decreases due to genericization, overall, per patient cost decreased to $135,400 (calculated similarly as the conventional CEA case). Adding new patient cohorts into the model further decreased the overall cost to $92,650, which was calculated as an average of the total costs across all patient cohorts, where each cohort was given an equal weight (Tables 5 and 6).

Finally, when also considering the increasing prevalence of the disease over time, the overall cost decreased to $91,099, reflecting that most patients affected by the disease will start the treatment in the future when the drug has already gone generic (Table 6 and Figure 5). This was calculated as a weighted average of each

Table 6: Comparison of overall per patient treatment costs between different model conditions.

Model condition	Factors considered			Average annual per patient costs	
	Genericization	Stacked Cohorts	Dynamic Prevalence	Simplified (10 cohorts and 40 year model)	Comprehensive (70 cohorts and 70-year model)
Traditional CEA (TCEA)	✗	✗	✗	$150,000	$150,000
TCEA considering generic entry	✓	✗	✗	$135,400	$135,400
TCEA considering generic entry and future patients	✓	✓	✗	$92,650	$19,980
Generalized CEA (GCEA)	✓	✓	✓	$91,099	$12,958

cohort's total costs with the weights being the normalized cohort size of each cohort (Table 5). When considering the full 70-year model horizon, the incorporation of genericization and future patient cohorts along with dynamic prevalence had an even more pronounced effect on the per patient average annual drug costs (Table 6). However, for cell and gene therapies, this effect on average annual drug costs may be more modest given these technologies may be less likely to go generic.

4.4 Option Value

Option value[5] occurs when a treatment's ability to either improve survival, health related quality of life, or disease progression allows patients to benefit from future innovations (Li et al. 2019, 2022). To better understand what option value is, consider a hypothetical patient who is diagnosed with non-small cell lung cancer. Assume that survival outcomes are poor among patients receiving the standard of care and a novel treatment – called OncoDrug – that extends patient survival for an additional year (12 months) has just come to market. When patients are considering taking this treatment, there are a number of *additional* treatments under development which could further improve but will come to market at a later date. In fact, consider the

5 Previous literature has named this value component "real option value" – to distinguish it from options developed in financial markets – but for brevity we have removed the word "real" and use "option value" throughout to refer to this concept.

case where eight months after the release of OncoDrug, a new breakthrough treatment – OncoCure – is released with superior efficacy. Despite the first treatment (OncoDrug) only improving patient survival directly by one year, patients who receive OncoDrug survive long enough to receive OncoCure, and therefore the true value of OncoDrug is much higher than one year of additional survival. In short, the health improvements enabled by the second treatment are only attainable for patients if they receive the first treatment and therefore a portion of the health benefits incurred from the second treatment represent the option value of the first treatment.

Generally, option value can be assessed via two clinical mechanisms: prolonged survival and slowing disease progression. Examples of prolonged survival models include those in cancer, amyotrophic lateral sclerosis, and similar diseases where the option value is derived from survival gains that allow patients to live long enough to see the new treatment approved. Option value models that slow irreversible disease progression to assess option value are relevant for some cancer treatments as well as degenerative neurological conditions like Alzheimer's disease, Parkinson's disease, and multiple sclerosis. By slowing disease progression, the initial treatment allows more patients to be eligible for future innovations which could help them maintain a better quality of life. In this case, patients who fail to receive the first treatment may progress to such as poor health state that the benefit of subsequent may be minimal.

Empirically option value can be measured from two perspectives: *ex ante* and *ex-post*. *Ex-post* approaches are more accurate and can be useful for future price negotiations, such as those that will take place under IRA (Arad and McClellan 2022). The *ex-post* methodology utilizes real-world data (e.g. claims-based data) to quantify changes in healthcare utilization and patient survival (Thornton Snider et al. 2018). For instances where GCEA is used in this context, an example can be found in Section 9.1.2. Yet, in many cases, economic evaluation occurs to estimate the value of upcoming or newly approved treatments.

Therefore, the real-world data required for *ex-post* analyses are not available to researchers conducting value assessment. Nor do they know what innovations will be brought to market in the future. For this reason, GCEA recommends utilizing *ex ante* option value which relies on a series of assumptions about the efficacy, time to approval, and probability of approval for future innovative treatments that could benefit patients in the future (Becker, Murphy, and Philipson 2007; Lee et al. 2022; Li and Garrison 2020). While this approach is less accurate, it is more useful for decision-makers as *ex ante* option value can be estimated at the time of treatment launch. Moreover, necessary parameters can be readily estimated from data on the clinical trial pipeline, public statistics published by the FDA and others, and peer-

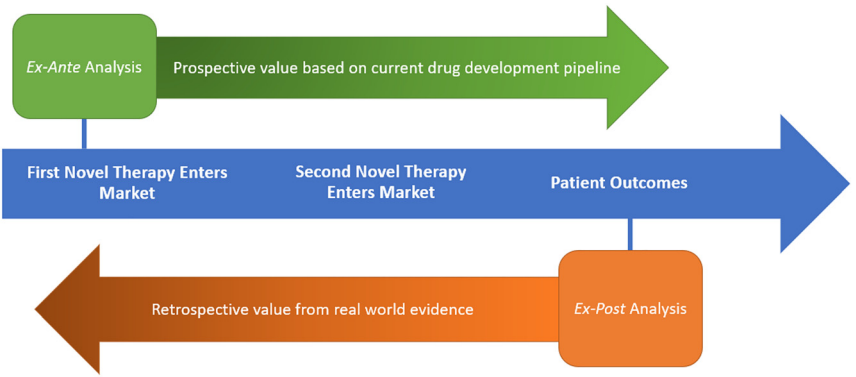

Figure 6: Conceptual differences in real option value methods.

reviewed publications. A key limitation of *ex ante* option value models is their reliance on stochastic parameters. Thus, a series of sensitivity analyses are required to address the underlying uncertainty of these parameter estimates. The differences in these approaches are summarized in Figure 6.

Option value provides non-trivial value in a variety of settings. In a study of the *ex-post* option value of ipilimumab in metastatic melanoma, patients diagnosed in 2013 experienced option value amounting to a 49 % increase in survival gains (Thornton Snider et al. 2018). Another study found that patients diagnosed with HIV/AIDS in 1995 and 1996 were willing to pay 400 % of the conventional value of azidothymidine therapy, because treatment with azidothymidine would allow them to access more effective highly active antiretroviral therapy later. In a separate, *ex ante* study of the option value of ipilimumab, incremental QALYs increased by 6.2 % while incremental costs only increased by 3.8 %, resulting in a 2.3 % decrease in the incremental cost-effectiveness ratio (Li et al. 2019). A separate *ex ante* study found that anaplastic lymphoma kinase gene-positive (ALK-positive) patients treated with first-line alectinib saw an increase in incremental QALYs of 12.9 % when accounting for the option value of the non-small cell lung cancer pipeline.

Implementing *ex ante* option value in practice requires four steps (Box 3). First, researchers should assess the time period when the focal drug would provide option value to patients. For example, if a clinical trial reports a 95 % confidence interval for a delay in disease progression, the mean value would be used to model the applicable time horizon for option value.

Second, researchers should forecast when the next innovative treatment targeting the same condition will become available to patients as well as its expected

Box 3: Overview of implementing *ex-ante* option value.

1. Determine plausible distribution of a recent innovation's (focal drug) time period for extending option value
2. Estimate the potential health benefits and costs of the future innovation using trend approach or pipeline approach
   - List therapies in clinical trial pipeline that target the same condition. Remove any that are likely to be equivalent to the focal drug
   - Forecast the arrival of future treatments that are not equivalent to the focal drug
3. Predict the probability and timing of approval as well as uptake conditional on approval of innovative treatment(s) in the future
4. Calculate option value as the increase in net monetary benefit of the advent of future innovation (step 1) based on the value of new treatment (product of step 2 and step 3)

costs and benefits.[6] For some diseases and treatments, such as Alzheimer's disease, where innovation is slow and current interventions do not provide substantial health gains, treatments may not provide option value to patients. If a disease, such as lung cancer, has a rapid development pipeline and existing treatments have proven efficacious, researchers should use available data on drug approvals to forecast how far in the future the next innovative therapy is likely to enter the market.

The future health benefits, costs, and arrival of the predicted innovation can be forecasted by using either the trend or pipeline approaches (Figure 7). The trend approach forecasts survival and health-related quality-of-life trends based on their past trends on clinical outcomes and the demographical changes of the target population. Although this approach utilizes a variety of sources to produce robust projections of future efficacy, it is ultimately data intensive and relies upon the assumption that future trends can be predicted from past data. The pipeline approach requires early (or late if possible) clinical trial results and manufacturer pipeline data to forecast which treatments may become available to patients within a relevant time horizon and how effective the future treatments will be. This method assumes that the observed efficacy in early clinical trials is representative of the treatment's true clinical benefit upon approval.

The third step predicts the probability of treatment approval, the timing of approval, and real-world uptake (conditional on approval) for the future treatment. The probability and timing of approval can be obtained from literature-based estimates. For the uptake rate, one can use real-world data from disease analogs to

6 Potential future innovations should be listed, but future treatments that are likely to be equivalent to the focal drugs of interest should be removed from consideration. Clinical expert opinion could be used to evaluate likelihood of therapeutic equivalence.

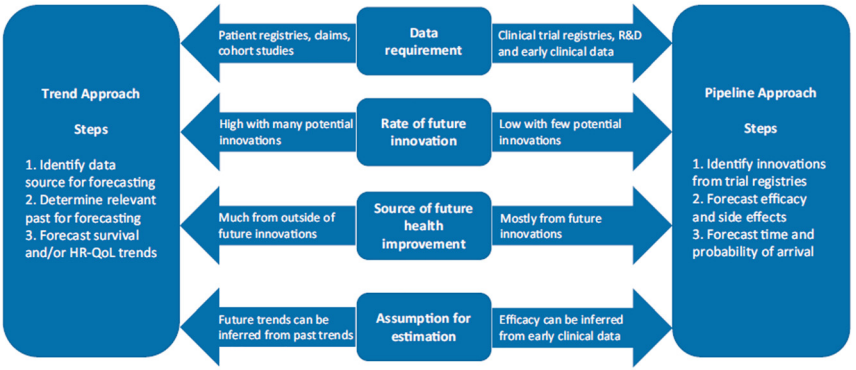

Figure 7: Forecasting innovation for *ex-ante* option value.

estimate the likely speed at which new innovations are adopted. Additional precision can be gained by adjusting the expected time of arrival through the use of surrogate endpoints and special regulatory designations, such as orphan drug or breakthrough designations.

Finally, option value is calculated as net monetary benefit after allowing patients to begin utilizing the novel treatment in the future based on the expected value of the health benefit of the innovation. As *ex ante* option value largely relies on the stochastic parameters such as the likelihood of regulatory approval, the expectation of efficacy, the predicted time to market entry of new medical technologies, etc., it is imperative to confirm internal validity by conducting sensitivity or scenario analyses. A numerical example can be found in Section 9.1.

Incorporating option value into GCEA requires minimal changes to the overall model structure. At the time of expected arrival of the new treatment (determined in step 1 of Box 3) conditional on the specified probability of approval (determined in step 3 of Box 3), patients who are alive and eligible will begin to receive the new treatment. These patients, in both the treatment and comparator groups, will receive the health benefits (and incur subsequent costs) of the innovation (determined in step 2 of Box 3). In addition, option value can be combined with dynamic prevalence by running Monte Carlo simulations to model how patients who took the focal drug in subsequent year's cohorts accrue option value.

4.5 Scientific Spillover

Treatment innovations provide value to society through knowledge spillovers or "scientific spillovers" that manufacturers can build upon to make future innovations.

In fact, pharmaceutical firms routinely build on insights obtained from previous drug innovation, both successful and failed attempts. For example, the testing of compactin – the first cholesterol-reducing statin that was tested in animals in the 1970s – was discontinued due to the drug's safety concerns. However, compactin's failure did not mean the new statin class was without potential. After analyzing the issues, Merck determined the safety issues were specific to compactin but that the drug class still looked promising. Therefore, Merck resumed its own development of a chemical analog to compactin. That effort resulted in the approval of lovastatin, which then spurred further development of other chemically similar statins including simvastatin and atorvastatin (Frankel et al. 2023).

Moreover, these knowledge spillovers can also occur across different therapeutic classes; for instance, treatments for one autoimmune disease can incentivize treatment innovation for multiple different autoimmune diseases (Xie et al. 2022).

In other words, both failed and successful drug development efforts can generate new knowledge that catalyzes follow-on drug development that might prove even more valuable than the predecessor drug candidate. While a drug's structural differentiation is not a direct source of value, novelty indirectly creates value as a source of exploration. Applying an old drug to a new disease area, new biological target, or new combination therapy, might also generate new scientific evidence that helps open up new avenues for research and/or new drug classes.

While the scientific spillover petal make sense intuitively, recent research has quantified the impact of scientific spillovers in the real world. Frankel et al. (2023) utilized the Tanimoto score – a measure that quantifies the share of chemical features a drug has with previously approved molecules – to link drug novelty to spillovers; using this score, the authors determined the number of successor drugs inspired by a focal drug and then calculated the sum of these successors' annual revenues as the focal drug's scientific spillover (Frankel et al. 2023). Moreover, the study demonstrated that more novel drug candidates generated larger spillovers than less novel drug candidates, even though novel drug candidates are themselves less likely to reach the market.

However, these methods have significant limitations for their use in CEA; the described method does not measure spillovers to health benefits directly, and the Tanimoto score is not applicable to biological drugs. While the former challenge remains underdeveloped in literature, the latter can be resolved using alternative methods that consider all drug types. Lanthier et al. (2013) developed an approach to group all new drugs into classes – based on FDA pharmacologic classes and the original indications of the drug – and to qualitatively measure the novelty of drugs within these classes as either "first-in-class" (first drug developed in a drug class), "advance-in-class" (drug provides major advancement in its class), or "addition-to-class" (drug is an incremental innovation) (Lanthier et al. 2013).

Alternatively, drug novelty can be measured on an order-of-entry basis for drugs, where drugs are grouped into classes with similar mechanisms of action and earlier drugs within these classes can be considered as more novel. Finally, one can extend the drug similarity method to biologics using historic pipeline data. For biologics with a novel target, the analyst could calculate the expected number of total/successful follow-ons based on the histories of novel biologics in similar disease areas.

We recommend that a new drug's knowledge spillovers are incorporated into GCEA qualitatively by discussing the degree of drug novelty and likelihood of inspiring follow-on R&D (Box 4); scientific spillovers will not be directly incorporated into the estimate of treatment value, but should be analyzed by researchers (Frankel et al. 2023). Researchers can measure drug novelty using the methods described above or through expert clinical opinion; when possible, we recommend measuring novelty quantitatively using chemical similarity scores (e.g. Tanimoto) or based on the development entry order into a specific biological mechanism-of-action. Such measures provide an objective approach in measuring drug novelty compared to previous methods, which largely relied on the frequency of relevant patent citations (Frankel et al. 2023; Lanthier et al. 2013).

Qualitative assessments might further incorporate information about scientific excitement around a particular new drug or mechanism. How many scientific papers and distinct author groups publish papers during the development of the novel drug? If the scientific exploration around a novel drug target extends beyond the sponsoring pharmaceutical firm, the drug's development is likely to generate knowledge and development spillovers beyond that focal drug – regardless of whether the focal drug succeeds in trials.

While more research is needed before implementation, researchers could alternatively consider adjusting the CE threshold used to value health gains in GCEA

Box 4: Overview of potential approaches for implementing scientific spillover into GCEA.

Qualitatively analyze potential knowledge spillovers as a contextual factor of GCEA. Analysts should analyze drug novelty and potential for scientific and R&D spillovers

1. *To measure novelty*, calculate the Tanimoto chemical similarity of the drug of interest to predecessor drugs; rank drugs order of development entry to a pharmacological class or disease-biological target pairs; or group drugs based on "first in class" (most novel), "advance in class," or "addition-to-class" (least novel)
2. *To estimate the likelihood of follow on drug development and scientific research* attributable to introduction of the focal drug, researchers can examine the number of follow-on development programs inspired by similarly novel drug candidates in same/similar disease areas

to increase by larger amounts for more novel drugs to reflect the drug's larger spillover effects. Adjusting the CE threshold in this way reflects the fact that while more novel drugs can provide larger spillovers, these drugs are often riskier to successfully develop (Frankel et al. 2023); CEA should assign greater value to more novel drugs – beyond just their potential to bring larger patient health benefits – to reward and incentivize manufacturers for more novel innovations. This improves the efficiency of resource allocation by having the positive externality innate in a firm's R&D investment decision-making process.

Moreover, as another alternative to the described approach, researchers could also estimate and incorporate a drug's qualitative level of scientific spillovers into CEA based on its relative novelty using multi-criteria decision analysis (MCDA) (Gongora-Salazar et al. 2023; Phelps and Madhavan 2017; Thokala and Duenas 2012; Thokala et al. 2016). Using MCDA when groups are the decision-maker requires an additional expertise in social choice theory (Phelps and Madhavan 2021). While estimating the scientific spillovers value component is real, due to significant uncertainty in terms of approaches for forecasting this value and uncertainty around how a CE threshold could be adjusted, at this point we recommend including scientific spillover in a decision-maker's set of contextual factors.

4.6 Societal Discount Rate

Discount rates are used in value assessment to indicate societal preferences for health benefits that occur sooner (rather than later) and to defer costs into the future. Observed human behavior provides an empirical and economic rationale for discounting both health costs and gains in health technology assessments, as surveyed people express a preference for benefits to accrue in the present and costs to occur in the future (Claxton et al. 2006; Gravelle and Smith 2001; Johannesson and Johansson 1997; Parouty et al. 2014). People who elect to invest in their future health face a clear opportunity cost by exchanging consumption of other goods and services for improved health (Claxton et al. 2006).

In recent years, conventional CEA practitioners most frequently employ a constant 3 % discount rate on both health benefits and costs. The practice of applying equal discount rates to health costs and benefits ensures that two interventions initiated at separate times, but with equal costs and benefits, will receive equal priority if the value of health is constant over time (Jit and Mibei 2015). The use of a rate of 3 % is often justified because past assessments utilize a constant rate of 3 %, and therefore future studies should do so as well to maintain comparability. In addition to academic precedent, many HTA bodies (e.g. NICE, ICER) recommend the use of a 3 % discount rate.

While important to reflect temporal preferences and promote comparability, the use of discount rates (and in particular the rate selected) has a significant impact on treatment value, particularly when costs and benefits are asynchronous. For example, pediatric indication and vaccine treatment benefits accrue over time, while treatment costs are a one-time event in the present period. In this case, standard discounting can significantly reduce the perceived health benefit compared to costs. The changes in the discounted QALYs and ICER in Table 7 are adapted from a CEA for human papillomavirus vaccination (Westra et al. 2012). The costs of vaccination take place in the present period for this study, while the benefits of immunity accrue well into the future. Under conventional, constant universal discounting of costs and benefits at a rate of 3 % (as used by most value assessments), the ICER increases by nearly five times the undiscounted value.

GCEA recommends using an empirically derived societal discount rate based on the positive approach or the normative approach, rather than simply following previous precedent (Box 5). The positive approach considers health as a tradable asset and therefore spending on healthcare can be interpreted as an investment in an asset whose opportunity cost should be compensated by future returns in health, represented by a risk-free interest rate. In a survey of experts on social discounting,

Table 7: Effects of discounting HPV vaccine health benefits and costs, by rate and method (Westra et al. 2012).

Discounting approach	Discounted QALYs gained	ICER (€/QALY)	Percent change in ICER
Undiscounted	3,462	7,600	–
Constant 1.5 %	1,423	18,400	142.1 %
Constant 3 %	715	37,000	386.8 %
Constant 4 %	438	59,100	677.6 %

Box 5: Overview of societal discount rate best practice.

1. Select either the positive approach or normative approach:
   a. Positive approach – Risk-free real interest rate, aligned with model horizon
   b. Normative approach – Ramsey Equation
   c. Use 2.0 % in the base analysis and 1.0 % – 3.0 % in sensitivity analyses
2. Justify the **method and rate** selected for use in value assessment
3. Examine different discount rates in the scenario and sensitivity analyses

the median reported value of the risk-free rate was 2 %, but suggested values ranged from between 0 % and 6 % (Drupp et al. 2018).

To employ the positive approach, the literature recommends utilizing the real rates of return on government bonds as a proxy to the risk-free rate. The rate selected should follow the time horizon specified within a value assessment. For example, if a lifetime horizon is used (commonly assumed to be 30 years), the 30-year rate on government bonds should be used as the discount rate. Although bond yields have in the past been consistent with a recommended annual discount rate of 3 % percent (e.g. when the Second Panel on Cost Effectiveness in Health and Medicine published their guidance in 2016), a trend toward lower *real* bond yields suggests an annual discount rate of 2 % for health technology assessment is now appropriate (Cohen 2024).

The normative approach utilizes the Ramsey equation to derive the societal discount rate that attains Pareto efficiency in an intertemporal optimization problem. The Ramsey equation implies that in the steady state of the Ramsey-Cass-Koopmans neoclassical model, the long-term social discounting factor (or the opportunity cost of the investment in the risk-free capital, i.e. risk-free rate) should be equivalent to the optimal rule of the intergenerational distribution of the marginal return on the risk-free capital. The determinant factors of the (extended) Ramsey equation include (i) societal pure time preference, (ii) wealth effect, which is a product of the consumption growth and risk aversion, and (iii) the precautionary effect which explains the uncertainty in consumption growth (Drupp et al. 2018).

The Ramsey equation is a useful alternative to the positive approach, despite some discussion of the limitations. First, uncertainty exists among several key determinants of the optimal discount rate such as the annual consumption growth rates, elasticity of the marginal utility with respect to consumption, and volatility of economic growth. Moreover, in a survey of economic experts, there existed significant differences between the rates calculated through the Ramsey equation (median = 3 %) and responses by the economic experts on their perceptions of the correct social discount rates (median = 2 %) (Drupp et al. 2018). This implies the Ramsey equation may not in fact be preferred in practice, but some additional research is needed.

Researchers may also use a combination of the positive and normative approaches to implement a societal discount rate within GCEA. In a survey of economists, 92 % determined that the societal discount rate fell between 1 % and 3 % with a median rate of 2 %(Drupp et al. 2018). This aligns with the 30-year rate suggested by the positive approach. Because model horizons may differ from 30 years and market conditions may evolve, if researchers use a 2 % rate at baseline it should be supplemented with sensitivity analyses utilizing rates between 1 % and 3 % (Drupp et al. 2018). Importantly, projections of slowing consumpton growth rates

suggests that the all-important wealth effect term on the right side of the Ramsey Equation is decreasing, pointing to a lower discount rate based on the Ramsey framework (Cohen 2024).

Because the social discount rate depends on the societal preferences for trading off near-term and long-term health benefits and costs, there is no single theoretically supported consensus on a particular discount rate to use in health technology assessments. Therefore, researchers should justify why a particular discount rate and method are selected.

5 Beneficiary

5.1 Patient-Centered Health Improvements

Making health value assessment more patient-centered has been a goal for many organizations, from patient advocates to researchers and beyond. Existing methods incorporated into conventional CEA often fail to capture a patient's experience navigating treatment options. As the concept of patient-centeredness evolves, patients and other stakeholders must be engaged throughout both the treatment process as well as the establishment of best practice guidelines. Within GCEA, a central principle of the Patient-Centered Health Improvements petal is that the measurement of survival gains should not discriminate against those with disabilities.

Patient-centeredness faces a fundamental challenge: value assessment evaluates treatments at the population level, but treatment value may be unique for each person. For instance, some patients may prefer cancer treatments that extend survival regardless of the severity of adverse events incurred; for other patients, quality of life is paramount, even above and beyond survival gains.

While fully patient-centered health improvements are a multi-faceted challenge and will vary across diseases, GCEA argues that any quantitative measure of estimating the magnitude of health benefits should ideally capture at a minimum four key components. First, the measure should be built on microeconomic theoretical foundations. In other words, the specific health benefit measure should come from a conceptual framework based on *individual* patient preferences. Second, any metric used to measure health benefits should capture both quality-of-life and survival gains. Third, the health gains for patients with more severe diseases should be valued more than identical health gains for less severe diseases, as multiple studies have found that individuals are willing to pay more for identical QoL gains when these QoL gains occur from more severe disease states (Bleichrodt et al. 2003; Gyrd-Hansen 2005; Nielsen, Gyrd-Hansen, and Kjær 2021). Finally, survival gains should not

discriminate against the disabled. Many health benefit metrics value life extensions less when these life extensions occur in a lower quality-of-life health state.

In the conventional CEA framework, the standard QALY approach has been used to measure health benefits. However, it possesses several limitations. First, although the use of the QALY is rooted in micro-theoretic foundations, it relies on an assumption of patient risk neutrality, which makes the QALY deviate from patient-centered sources of value (Lakdawalla and Phelps 2020). Since solving for the utility maximization problem under the risk-neutrality assumption, the conventional CEA framework equates the marginal gains in utility with those in health which are represented by QALY gains. However, it is typically assumed that patients are risk averse and thus, the conventional CEA based on the QALY approach does not give the true value of a treatment. Second, the standard QALY approach values all quality-of-life gains equally no matter what the disease is severe, or the baseline health of patients is poor (Bleichrodt et al. 2003; Gyrd-Hansen 2005; Nielsen, Gyrd-Hansen, and Kjær 2021). These may underestimate the value of a treatment of a severe disease or that for patients with low health endowment such as disabled or elderly.

The efforts to make value assessments patient-centered include life-years gained, decision modifiers, equal value life year (evLYG), and more recently the GRACE framework through GRA-QALY (Campbell, Whittington, and Pearson 2023b; Excellence 2022a; Luo et al. 2009). GCEA evaluates each approach by four criteria (Table 8).

Table 8: Comparison of frameworks for addressing patient-centered health outcomes.[a]

Measure of Health Benefit	Factors Considered			
	Based in micro-theoretic foundations	Incorporates QoL and survival gains	QoL gains for severe disease valued more	Survival gains for disabled equivalent to able bodied
QALY	✓*	✓	✗	✗
LY	✓+	✗	✗	✓
Decision Modifiers	✗	✓	✓-	✗
evLYG	✗	✓	✗	✓
HYT	✗	✓	✓	✓
GRACE	✓	✓	✓	✗

[a] *Yes, if patients are risk neutral. +Yes, if treatment has no QoL implications. –Yes, if QALY shortfall is met.

Analyses based on life-years gained simplify the health benefit of treatment by considering the survival benefit of treatment in isolation. Instead of weighting patient survival by their quality of life, life-year gained analyses sum patient survival gains to evaluate health benefit. By evaluating treatment benefit in terms of survival, life-year gained analyses value health benefits equally regardless of a patient's baseline disability. By construction, life-year gained analyses exclude quality-of-life improvements that result from treatment. This implies that these analyses do not recognize the additional value of treating severe disease when treatments improve patient quality of life, despite being a source of value for patients. Life-years gained thus only aligns with microeconomic theory if and only if a treatment provides no quality-of-life benefit or patients do not care about quality-of-life gains (unlikely). Furthermore, life-year gains can be limited by factors unrelated to treatment efficacy, such as patient age and disease-specific mortality risks.

The equal value life year (evLYG) metric aims to address some of the limitations of the life-years gained metric and of the QALY metric by evaluating survival gains at a highly favorable, and uniform, assumed quality of life during periods of life extension. In the evLYG approach, additional life years are weighted by a QoL of an average individual within the general population (0.851) regardless of actual patient disability (Campbell, Whittington, and Pearson 2023b; Luo et al. 2009). The evLYG metric differs from life-year gained analyses because the evLYG considers the quality-of-life gains of treatment during periods of shared life, and only remains agnostic of disease severity or baseline disability during the additional survival gains period. By assuming the quality of life is the same during life extension for all conditions and individuals, the evLYG attempts to align treatment valuation with priorities for treating life extension equally (Nord et al. 1999; Representatives 2010; Rodgers 2023).

Although multiple CEA studies have included the evLYG, the decomposition and subsequent unequal weighting of health gains due to quality of life and survival is not based in microeconomic theory, and evLYG violates the weak and strong forms of the Pareto principle (Lin et al. 2023; Review 2023a, 2023b). As a result, evLYG biases value assessments against treatments that primarily improve patient quality of life in life extension. *Additionally*, the quality-of-life gains measured by evLY are assessed agnostic of disease severity or patient baseline health endowments. Finally, debate exists on the true willingness to pay for an evLYG or life-year gained and a range of estimates exist in the literature (Acaster et al. 2013; Campbell, Whittington, and Pearson 2023a, 2023b; Lakdawalla et al. 2018; Lakdawalla and Phelps 2020, 2021; O'Day and Mezzio 2021; Sawhney and Thakur 2023).

The Health Year in Total (HYT) metric attempts to address the limitations of the QALY by measuring patient health improvements on an additive scale (Basu et al. 2020). Similar to evLYG, HYT decomposes health gains into incremental life-year gains and QoL gains. However, rather than measure QoL gains over the period of survival in the comparator arm, HYT evaluates these gains for the total number of LY in the treatment arm. To do so, HYT makes two axiomatic assumptions. First, HYT assumes utility independence such that patient preferences over survival gains under uncertainty are not dependent on the quality of life enjoyed during survival, nor are preferences over QoL gains dependent on fixed longevity intervals. Second, HYT assumes a constant proportional tradeoff between QoL and life-years and as a result a patient's marginal rate of substitution between additional survival and additional QoL is independent of that patient's remaining life years. As a result of these assumptions and the additive framework used to construct HYT, the number of HYTs a patient can gain in a given year ranges from 0 to 2.

HYT – like evLYG – may be especially attractive for health technology assessment by CMS under the IRA since May 3, 2024 guidance documents states that QALYs cannot be used to inform maximum fair prices (Centers for Medicare and Medicaid Services 2024); however there are some potential logical inconsistencies that researchers who use HYT would need to be aware of. First, HYT can violate the independence of irrelevant alternatives axiom that is a fundamental pillar of rational choice theory, because survival gains in the comparator arm are dependent on the survival properties of an alternate, mutually exclusive treatment (the intervention) (Paulden et al. 2024). Second, the use of QoL estimates to compute patient utility requires that patients are alive and thus the counterfactual QoL in the comparator arm relied upon by HYT violates this definition. Third, HYT assumes that patients who experience additional survival experience the same QoL that they had prior to the period of additional survival. However, patients experiencing additional survival may have poorer health during survival compared to the health related QoL, among the alive, in the comparator arm. Fourth, empirical estimates suggest that HYT's assumption of constant proportional tradeoffs is violated when patients are risk averse, as a patient's marginal rate of substitution is correlated to their health allocations and risk preferences (Lakdawalla and Phelps 2022, 2020). Finally, additional research is required to establish cost-effectiveness thresholds for an additive scale, such as HYT, and at the time of publication the authors of this paper are unaware of any health technology assessments relying upon HYT to measure health gains (Basu et al. 2020).

Rather than replacing the standard QALY, NICE issued guidance on implementing decision modifiers in the assessment of rare and severe diseases. These modifiers increase willingness to pay for the treatment of severe disease if an indication meets a QALY shortfall threshold (Excellence 2022a). NICE defines

absolute QALY shortfall as the difference in the level of QALYs to individuals with disease compared to the number of QALYs to comparable individuals (i.e. individuals with similar demographics) without the disease. If a disease meets this definition of severity, a scalar multiplier is applied to the modeled willingness to pay for a QALY to approximate the additional treatment benefit of treating severe disease. Because decision modifiers rely upon the QALY to initially calculate health benefits and QALY shortfall, modifiers incorporate both quality-of-life and survival gains in computing patient-centered health outcomes.

However, decision modifiers contain a number of limitations which make them poorly suited for implementation in patient-centered value assessment frameworks. First, they do not address all severe diseases, particularly those affecting older populations. For example, Alzheimer's patients (who have an average age of onset of 80 years old for sporadic AD) are drawn from a population of patients with low expected QALYs and therefore do not meet the required thresholds for implementing severity modifiers. Second, the literature has also criticized severity multipliers for often being politically driven and containing logical inconsistencies (Paulden et al. 2014).

Rather than addressing the value of treating severe disease systematically, the decision to utilize a multiplier as well as the magnitude of the multiplier selected is often made arbitrarily. A consequence of this is an increased opportunity cost for other patient populations, whose treatments may already be undervalued due to bias against disability. For example, drugs approved under NICE's end-of-life multiplier delivered an annual 12,401 QALYs to late-stage cancer patients but had an opportunity cost of 18,330 QALYs to patients with other diseases (Charlton 2023).

On the other hand, the GRACE framework uses a qualified patient-centered health benefit metric, GRA-QALY. The quality-of-life gains of GRA-QALY is a function of certainty equivalent obtained by relaxing the risk-neutrality assumption, which better fits consumer choice theory. Also, the GRA-QALY incorporates not only the quality-of-life gains but survival gains, which are calculated using the exchange rate between life years and QALYs. GRA-QALYs are monetized using RASA-WTP which models patients' increased willingness to pay for health gains for severe disease. Furthermore, the monetary value of the GRA-QALY gains can address the issue of the conventional CEA regarding discrimination against individuals with poor health (e.g. disabled, elderly) because RASA-WTP additionally accounts for permanent disability at the baseline period.

Rather than use methods that inconsistently or incompletely address the multiple dimensions of patient-centered care, GCEA recommends using GRACE to incorporate additional value from patient-centered health outcomes. To address any potential limitation of GRACE, GCEA additionally recommends conducting life-year

gained analyses as a sensitivity analysis. A discussion of implementing GRA-QALYs can be found under Section 3.4.

5.2 Equity

Cost effectiveness approaches – such as both conventional CEA and GRACE – capture treatment benefits to patients but often ignore how health benefits accrue differently across heterogenous patient populations. Aside from the additional value to patients of reducing health disparities across patient subgroups, there is a clear societal value in improving health equity. Numerous studies have demonstrated societal preferences for placing a higher value on health gains for disadvantaged individuals. Policy decisions (e.g. the creation of Medicaid and Federally Qualified Health Centers for low-income individuals) also suggest that society has strong willingness to pay for increased health equity (Lakdawalla et al. 2018). The passage of the Affordable Care Act expanded insurance access to an estimated 29 million US residents, many of whom represented minority groups. Because of the societal eagerness to promote equity considerations across institutions, health disparity reductions provide additional treatment value to be considered in value assessments.

Consider the case where there is a hypothetical disease called "billionaire-itis" which causes depression in the wealthiest of individuals and another disease called "low-income depression" which only occurs in individuals at the bottom of the wealth distribution. If treatments for both diseases came to market with identical safety and efficacy, conventional CEA would value each treatment equally. However, many members of society would say that the treatment for "low-income depression" patients should be valued more than the treatment for "billionaire-itis" because low-income individuals have relatively worse health outcomes at baseline. As such, the use of the new treatment for "low-income depression" would help reduce health disparities and add to societal value; conversely, the treatment for "billionaire-itis" would exacerbate health disparities, which would attenuate the treatment's value to society.

Healthcare disparities inspire constant policy debate, with efforts such as the Affordable Care Act adopted to expand care access to under-represented groups. More recently, the COVID-19 pandemic renewed interests in health inequity, as many minority communities were disproportionately impacted by the pandemic. From a healthcare resource utilization perspective, Black and Hispanic individuals often report the highest rates of cost-related delays in care and lower access to high-quality medication. Furthermore, studies assessing health disparities in oncology have found that low socioeconomic status is correlated to poor access to high-quality care, lower screening rates, delays in treatment after diagnosis, and lower treatment

adherence–all of which result in diminished patient health outcomes. As a result of these disparities additional benefit of medical innovation is derived from a treatment's ability to reduce health disparities.

To incorporate the value of reduction in health inequality within a unified value framework, GCEA recommends using distributional cost-effectiveness (DCEA) (Box 6). DCEA enables researchers to estimate the health benefit of treatment while accounting not only for health disparities but financial disparities that exist between patient subgroups. DCEA relies upon societal preferences for reducing health disparities, and as a result awards more value – compared to conventional CEA – to treatments that disproportionally benefit underprivileged patient populations (Love-Koh et al. 2019). Societal preferences for reducing health disparities can increase the value of treatment by up to 3.38 times as many QALYs per patient (Love-Koh et al. 2019). In a study assessing mandates for lung cancer screening, approximately half of the treatment value was attributable to reductions in health disparities. Health equity improvements due to funding COVID-19 treatments resulted in a population-level health effect of more than 130,000 QALYs (Kowal et al. 2023).

Implementing DCEA to evaluate health equity in a US context requires a multi-step approach and the literature provides well-founded assumptions for where

Box 6: Overview of DCEA implementation.

1. **Choose groups**:
   Define patient sub-groups based on health disparities documented in the literature
2. **Measure costs and benefits of treatment for each group**:
   For each identified sub-group, use a standard CEA model to compute the costs and benefits of treatment and comparator
3. **Calculate incremental net health benefit by group**:
   For each identified sub-group, calculate the net health benefit in the treatment and comparator arms. Net health benefit is equal to QALYs plus costs converted into QALYs using the cost from (2) divided by the willingness to pay for a QALY
4. **Estimate quality adjusted life expectancy (QALE) before and after intervention for each sub-group**:
   For each sub-group, compute QALEs in the treatment and comparator arms by adding the net health benefit of treatment from (2) to the baseline QALE's for each group in the general population
5. **Calculate equally distributed equivalent (EDE) QALYs**:
   Select inequality aversion parameter. Compute EDE QALYs for treatment and comparator groups using the Atkinson or Kolm social welfare function
6. **Use EDE QALYs to measure value with standard approaches:**
   Resulting incremental EDE QALYs represent the total value of treatment including the value of reducing health disparities

parameter data is lacking (Kowal et al. 2023). Box 6 provides one set of potential steps, but implementation can vary using the numerous methodologies available. Consider, for example, that we want to incorporate the societal value of a new treatment developed that cures lung cancer for patients with a history of smoking and tobacco use. Assume that among lung cancer patients there are two patient populations of smokers, wealthy smokers and poor smokers, and that the literature has documented that wealthy smokers have better outcomes at baseline than poor smokers.

The first step of DCEA is to identify and justify the selection of equity-relevant subgroups of patients based on demonstrated health inequities in the literature (Kowal et al. 2023). In the United States, evidence exists on baseline health disparity across race, ethnicity, and geography, but researchers should consider additional strata such as income quintile, level of educational achievement and other patient characteristics or combinations of traits relevant to the condition or population of interest. A number of indices exist for measuring health disparities, such as the social vulnerability index and more recently developed social vulnerability metric. ICER has developed the health improvement distribution index (HIDI) to examine differences in the composition of patient populations; but HIDI is an aggregate measure of representativeness, not a measure of disparities, and HIDI cannot be used in DCEA. Unfortunately, a variety of data needs exist to implement DCEA to inform healthcare decision-making in the US context. For example, mortality and baseline QALY data is unavailable for many races, ethnicities, as well as for Americans residing in rural areas. Furthermore, clinical trials used to assess treatment efficacy are often not representative of all types of patients while poor real-world evidence exists on patient outcomes across heterogenous patient populations.

Second, once sub-groups are selected, a conventional CEA model is used to calculate the group-level incremental QALYs and costs for both the intervention and comparator arms of the model.

Third, after calculating sub-group costs and benefits, the results are used to compute the subgroup-level net health benefit (NHB) of the intervention and comparator groups, which takes the form shown in (Equation (6)):

$$\mathrm{NHB}_{g,s} = \Delta\mathrm{QALY}_{g,s} - \frac{\Delta\mathrm{Costs}_{g,s}}{\mathrm{WTP}} \tag{6}$$

Where g denotes the subgroup, s represents the intervention or comparator group, and WTP refers to the standard willingness to pay for a QALY.[7] In the example of a treatment that cures lung cancer in smokers, one would simply apply the treatment benefit in a conventional CEA framework but use subgroup-specific measures of

7 Generally assumed to be $100,000 per QALY.

quality of life, pharmaceutical costs, comparator clinical efficacy, medical costs and societal costs. For example, poor smokers may have worse overall quality of life due to untreated comorbidities or experience difficulty taking time off from work to receive regular infusions.

Fourth, researchers should select an appropriate inequality aversion parameter based on their model setting and leverage the sub-group specific data to estimate the opportunity costs for each patient subgroup. The most widely used metric for measuring health outcomes at baseline is quality-adjusted life expectancy (QALE). QALE represents a patient's expected QoL accumulated over the duration of their survival. This differs from a QALY, which measures the direct health benefit accrued to a patient after getting a disease; instead, a QALE measures the quality-of-life-adjusted life expectancy for individuals from birth. To calculate subgroup-specific QALEs of the intervention and comparator groups, the baseline QALEs of each subgroup need to be calculated first by taking a weighted average of the subgroup, age-specific QoL. Age-specific QoL estimates can be obtained from publicly available data sets of healthcare survey data (e.g. Medical Expenditure Panel Survey), where the weights are the subgroup age-specific survival rates from the US Census data. Returning to the example of poor and wealthy smokers, wealthy smokers may have longer life expectancy as they can afford more preventative care over the course of their lives, and higher age-related quality of life as they enjoy more vacations than poor smokers. By isolating baseline health expectations and sub-group specific net health benefit, researchers can calculate the expected impact treatment has for both wealthy and poor smokers individually. For intervention and comparator groups, the subgroup-specific QALEs are derived by adding the subgroup-specific NHB which is equally distributed to the general population of the subgroup (Equation (7)):

$$\mathrm{QALE}_{g,s} = \mathrm{QALE}_{g,\mathrm{Baseline}} + \frac{\mathrm{NHB}_{g,s}}{N_g} \tag{7}$$

where N_g represents the population size of the subgroup.

Fifth, for each of the intervention and comparator groups, calculate the equally distributed equivalent (EDE) QALYs. The EDE QALYs are analogous to the certainty equivalents discussed in Outcome Certainty; whereas certainty equivalent QALY gains incorporate risk preferences over uncertain outcomes, EDE QALYs incorporate inequality aversion preferences based on the distribution of health outcomes by group for both the intervention and comparator group. EDE QALYs are calculated using an Atkinson or Kolm inequality index, which estimates the social welfare resulted not only from the overall level of outcomes (QALYs in DCEA) of the general population but disparities (in terms of QALYs in DCEA) across subgroups or

individuals.[8] It is noteworthy that since NHB of each group is a function of opportunity costs of a treatment incurred to the group as well as health gains, the social welfare which is determined by the group-specific QALEs and the inequality index takes into account of the disparities by financial impact as well as by health impact. Once the preferred social welfare function is selected, researchers should select an accompanying inequality aversion parameter that is appropriate for their model setting and population. Consider, in the smoking example, that members of the general population strongly believe that poor smokers should enjoy the same access to cancer treatment as wealthy smokers. By applying a social welfare function to the QALEs of both wealthy and poor smokers, the additional societal benefit of curing poor smokers' lung cancer is incorporated into the modeled health benefit.

Sixth, the difference between the intervention and comparator group EDE QALYs represents the total value of treatment when reductions in health disparities are accounted for. These incremental EDE QALYs can be calculated using standard calculations leveraged in CEA. A numerical example can be found in Section 9.2.

The steps detailed here are one feasible way to implement DCEA. A variety of methods (e.g. aggregate DCEA vs. full DCEA) and indices available that one may select based on objective, data availability, condition, etc.

In theory, incorporating health equity effects into GRACE would follow the same steps outlined in Box 6 for conventional CEA. Researchers would begin by defining subgroups within the patient population following the first step of implementing DCEA. Next, GRA-QALYs and RASA-WTP can be computed through the GRACE framework and used to construct the group and scenario-specific net health benefit using the formula above. Finally, the group, scenario-specific net health benefits can be utilized with the same Atkinson or Kolm social welfare functions to generate EDE GRA-QALYs, which capture the health equity effects of treatments. While US-specific estimates of inequality aversion parameters are still under development, GCEA recommends a value of 10.95 derived from UK estimates. However, future research is needed to fully integrate DCEA into GRACE.

5.3 Family and Caregiver Spillover

While diseases directly impact the health and costs experienced by patients, patients' family members and friends are also affected by the financial and non-financial burdens of providing care. For instance, Alzheimer's disease patients frequently have informal caregivers (usually a spouse or close family member) who have been

8 The social welfare function selected will be determined by available inequality aversion parameters collected in step 4.

shown to incur high costs and disutilities as a result of providing care (Haro et al. 2014; Neumann et al. 1999; Robinson et al. 2020). Moreover, cancer caregivers often perform a diverse range of tasks – such as advocating for their patients, aiding in treatment decisions, and performing many nursing-related tasks with little preparation – and have been found to be vulnerable to emotional strain and distress, negatively impacting both their quality of life and productivity (Chiu et al. 2022). However, despite the existence of these non-trivial impacts of providing informal care, conventional CEA models often exclude these caregiver and family spillover and underestimate the value a novel treatment can bring to society by reducing informal caregivers' burdens (Grosse, Krueger, and Pike 2019a). ICER typically uses the payer or health system perspective as the base case and presents a modified societal perspective as a scenario analysis in most cases (Review 2023c).

Accordingly, GCEA recommends that caregiver and family burden elements are included into the base case in assessing the societal benefits of treatments, including the effect a treatment has in terms of caregiver QoL along with the treatment's impact on their experienced cost and productivity. First, researchers should determine the treatment's impact on caregivers' QoL and the number of caregivers impacted. While studies tend to examine the impacts on primary caregivers only (Wittenberg, James, and Prosser 2019), caregiving for certain conditions can also impact other family members as well (Bobinac et al. 2010; Wittenberg et al. 2013). Researchers should include multiple caregivers in their analyses when relevant.

To determine caregiver QoL benefits, caregiver QALY gains between a comparator and intervention case in GCEA can be calculated. One study utilized survey and regression methods to compare the annual QALY decrement between close family members who were exposed to patients experiencing the after-effects of meningitis (i.e. cognitive problems, motor limitations, behavioral problems, etc.) and those who were not exposed to these after-effects (Al-Janabi et al. 2016). Moreover, another study provides a review of alternative methods – such as the use of different QoL measures or considerations of effects beyond the primary caregiver – that can also be used to estimate the QALY spillover effect of a treatment (Wittenberg, James, and Prosser 2019). In fact, literature recommends using EQ-5D inputs to minimize double counting between the disutility of unpaid caregivers and the monetary value of caregiving time (Park et al. 2022).

Furthermore, analysts should also consider instances when caregiver QoL ratings do not correlate well with reported patient QoL, notably when caregivers are treating patients with severe dementia (Landeiro et al. 2020b). As such, after the caregiver QALY gains are determined, these will be valued separately from patients' risk-adjusted QoL and risk-adjusted longevity gains – captured as GRA-QALY gains within GCEA – and will be added together when determining the monetary value of the health benefits to society (Figure 8).

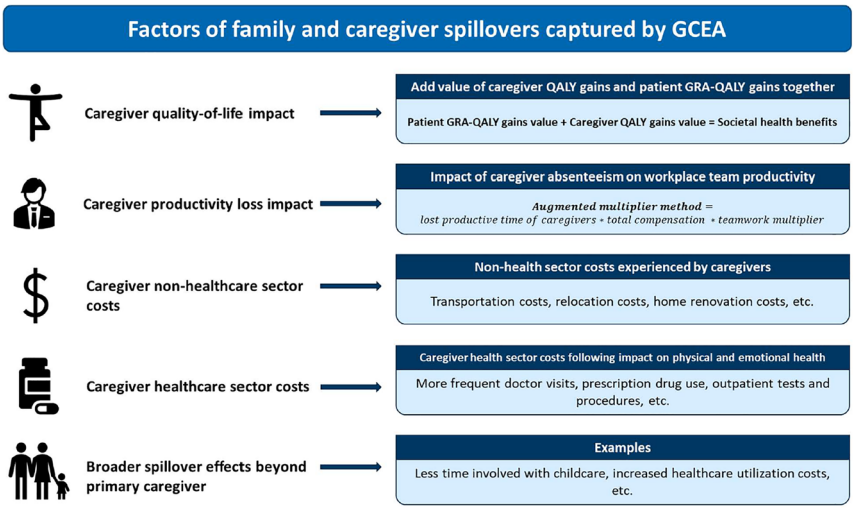

Figure 8: Overview of implementing family and caregiver spillover into GCEA.

Second, researchers should assess the treatment's impact on caregiver productivity, both on intensive (fewer hours worked) and extensive (exiting labor force) margins, which can be included into the cost side of value assessments. A majority of studies have estimated caregiver productivity costs as the time and wages forgone by informal caregiving. Yet, these methods only capture the partial impact caregiving can have on productivity, ignoring how employee absenteeism can have broader impacts to co-workers' productivity as well (Berger et al. 2001). Instead, following the methods outlined in recent literature, GCEA recommends researchers estimate caregivers' productivity losses using an augmented multiplier (Figure 8), which more comprehensively incorporates impacts on team member productivity and total compensation following caregivers' reduction in work hours or labor force exit (Chiu et al. 2022). These losses represent a social economic loss which can be alleviated by treatment benefits.

Third, separate from productivity losses, researchers should also incorporate the treatment's impact on non-healthcare sector costs – such as transportation, home renovation, and relocation costs – experienced by caregivers or family members to care for their loved ones (Mattingly et al. 2022). For instance, average monthly out-of-pocket costs for cancer *caregivers* ranged from $25 (breast cancer) to $1,223 (colorectal cancer), commonly covering expenses for care supplies, travel, and other accommodations (Coumoundouros et al. 2019). Fourth, researchers should also consider the healthcare sector costs caregivers experience due to challenges to their physical and emotional well-being caused by caregiver responsibilities

(Park et al. 2022). In fact, caregivers often experience anxiety and depression during informal caregiving – especially for those caring for patients with dementia – and are associated with more frequent use of prescription medications, doctor visits, and use of outpatient procedures ("2021 Alzheimer's disease facts and figures" 2021).

Finally, analysts may also consider broader caregiver spillover effects of the treatment (Figure 8). For instance, caregiving for a sick elderly parent may result in less attention or involvement towards the informal caregivers' children, which may adversely impact their children's future academic performance and social development (El Nokali, Bachman, and Votruba-Drzal 2010). A treatment that can reduce caregiver burdens can bring benefits to individuals beyond primary caregivers, and this should also be captured as societal benefits. Moreover, high caregiving burdens have been shown to lead to increased healthcare utilization by caregivers – including more frequent emergency department visits and provider visits (Goren et al. 2016) – which may lead to increases in healthcare costs experienced by society; treatments that can alleviate caregiving burdens have non-trivial value from their potential to reduce societal costs as well.

6 Additional Value Elements

While a number of additional value elements exist, four merit additional discussion for inclusion into the GCEA unified valuation inventory. The following section discusses these four elements: community spillover, productivity, adherence, and direct non-medical costs in turn.

6.1 Community Spillover

Conventional CEAs for infectious disease treatments largely focus on the direct health impacts experienced by individuals who get sick. However, individuals who are not infected by the disease can also be indirectly impacted, one case being fears of contagion that often lead to spillover effects to communities at large due to the anxiety of future disease spread. As a salient and recent example, individuals who never got infected with COVID-19 were still highly impacted by the closing of schools, closing of businesses, and travel prohibitions due to the mandated "lockdowns."(Ma et al. 2020).

As such, treatments that reduce infectious disease spread can provide substantial "community spillover" benefits to unaffected populations, and GCEA recommends that analysts consider these spillovers of treatments – when relevant – to capture their broader impacts on societal costs (Ma et al. 2020; McQueen et al.

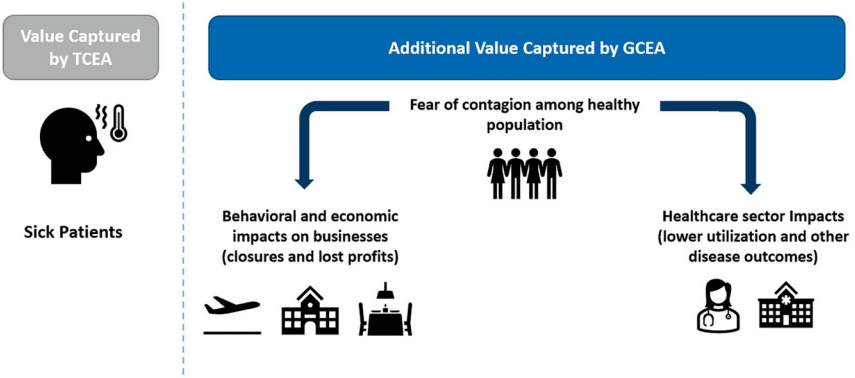

Figure 9: Overview of implementing community spillover into GCEA.

2024). Following methods provided by recent literature, these spillover impacts resulting from the fear of contagion can be measured on a per-capita basis through changes in the behavioral impacts on businesses (e.g. school closures and decreased public transportation), economic impacts on businesses (e.g. cancelled major events and restricted travel) and impacts on the health sector (e.g. less health-seeking behavior due to risk of exposure and considering health outcomes of other diseases) (Figure 9) (Ma et al. 2020) Moreover, non-medical costs associated with protection items against disease spread (i.e. masks, hand sanitizers, etc.) can also be included into community spillover estimates.

However, potential community spillovers are not limited to only infectious diseases. For example, treatments for hepatitis C that reduce the risk of patient's need for a liver transplant can increase the number of donor organs available to patients whose diseases cannot be cured yet, as hepatitis C is a major cause of liver transplants (Zahid 2022). Moreover, as recent campaigns have reduced hepatitis C rates by remarkable amounts (Hassanin et al. 2021), full elimination of diseases by treatments can also provide spillover benefits to all future populations who will effectively no longer be at risk for this disease.

6.2 Productivity

Treatments that mitigate patient productive loss carry an additional source of value beyond direct health benefits. The productivity impacts of poor health include reduced productivity at work (presenteeism), reduced ability to go to work (absenteeism), unemployment due to disease, productivity loss due to premature

death, and productivity gains of life extension. In accordance with ICER's 2023 value assessment framework update, productivity impacts should be included in the societal perspective whenever possible. These are obtainable from literature or can be estimated when direct evidence for the condition does not exist (Review 2023c).

Disease-specific productivity impact estimates can easily be incorporated into relevant GCEA frameworks, but often differ in their methods. For example, one study measured the productivity loss of patients with multiple sclerosis through reduced working hours, absenteeism, and early retirement from the workplace (Kobelt et al. 2000; Robinson et al. 2020). A separate study of Alzheimer's disease patients estimated the labor force participation rate of patients and the percentage of patients who claim to experience productivity losses due to their disease (Robinson et al. 2020). Recent efforts to generalize the productivity impacts of disease have extended this definition to include household production, non-household production, volunteering, and labor (Jiao and Basu 2023).

In addition to the standard productivity measures, there are some novel ways to capture productivity impacts that are less frequently used but valid, such as (i) non-labor income, (ii) spillover productivity impacts and (iii) macroeconomic impacts (Box 7).

For certain patients, non-market productivity (e.g. volunteering, looking after grandchildren) represents their primary source of economic output and therefore reductions in non-market productivity increase the burden of their disease. For example, one estimate in the literature found that patients aged 65–74 years generate 54.9 % of their economic output outside of labor markets (Grosse et al. 2019a). To capture this additional opportunity cost to patients, ICER's 2023 value assessment framework advised researchers to include both market and non-market productivity and to value the time lost in each category at the same wage (Review 2023c). However, a limitation to including both forms of productivity loss is the lack of available studies that provide robust estimates of non-market productivity. When disease-specific measurements of patient non-market productivity loss are not available to researchers, GCEA recommends an algorithm proposed in the literature to estimate non-market productivity by age and QoL (Grosse et al. 2019b).

Box 7: Novel forms of patient productivity losses due to disease.

1. Non-market labor income
2. Workplace spillovers (in teams)
3. Macroeconomic impacts and supply chain disruptions

Within market productivity estimates, spillovers due to patient productivity losses may occur when people work in teams. In team-based settings, patients' co-workers often also experience lower productivity due to their absence or lower productivity of their sick co-worker (or their co-worker who is a caregiver to a sick person, as noted above). For example, a factory employs workers on an assembly line where each individual specializes in the manufacture of a particular part of a larger good. When workers specialize, output is maximized across comparative advantages (Madiedo et al. 2020). If one worker has reduced productivity due to illness, they may lose their comparative advantage and the entire assembly line is reduced in its ability to produce goods. As a result, the illness of one patient has now affected the productivity of their entire team at work by more than the direct productivity loss related to their presenteeism and absenteeism.

When determining the value of productivity spillovers to teams, a teamwork multiplier can be constructed from existing literature estimates of substitution factors (measurement of how easily replaced a worker is by another) and team effect (measured as the percentage of time working on teams) (Nicholson et al. 2006; Pauly et al. 2002; Zhang et al. 2012). When team effects and fringe benefits are not included in productivity loss calculations, estimates of productivity loss were undervalued by 60–69 % of productivity loss for patients (Chiu et al. 2022).

Finally, some papers have estimated how illness impacts not only lower productivity at the individual and team levels but also the implications for the economy as a whole (Chen and Goldman 2018; Hafner et al. 2023). Namely, increased absenteeism and exits from labor force decrease the labor supply; decreased labor supply drives up wages in the broader economy and leads to reductions in gross domestic product (Hafner et al. 2023). Between 2000 and 2015 pharmaceutical innovation increased productivity in the US labor market by 5.5 million work days per year and $233 billion in wages per year (Chen and Goldman 2018). By comparison, in 2013 pharmaceutical net revenue for branded drug sales was $257 billion, implying that nearly all treatment costs were offset by societal productivity gains due to treatment (Hafner et al. 2023; Institute 2023).

6.3 Adherence

An additional element of value for new therapeutics is the degree to which they promote patient adherence, which allows more patients to benefit from treatment efficacy for longer durations. Ultimately, incorporating the adherence petal involves considering the possible divergence of an innovation's performance in the clinical trial setting versus how it might work in the real world. A long-acting injectable atypical antipsychotic for the treatment of schizophrenia may be no more effective than an oral in a controlled clinical trial setting, but real world evidence has shown

that adherence improves, discontinuation rates decline, and real-world hospitalization rates decline when using long-acting injectable atypical antipsychotics compared to daily oral medications (Kaplan et al. 2013; Marcus et al. 2015; Olivares et al. 2009).

Several factors have been identified to improve adherence, such as more convenient routes of administration, simpler dosing schedules, or combination treatments (Lakdawalla et al. 2018). Consider two treatments for a certain disease: the standard of care which requires inpatient infusions and a new innovation that allows treatment to be administered orally at home, once a day. Consider that for the population with this disease, driving to an infusion center for many patients is burdensome. The ease of administration for the new oral treatment may greatly improve adherence, as patients can administer the medication at home over a much shorter time period (swallowing a pill vs. a one-hour infusion) with limited transportation costs. This adherence-improving factor offers additional value to patients both through improvements in clinical outcomes and through additional utility due to convenience or tolerability.

For example, the enhanced effectiveness by the improved adherence not only increases the mean of future health outcomes of patients but reduces the uncertainty surrounding the outcomes. At the same time, for non-patients, it mitigates the impact of future disease risk (i.e. increases the value of disease risk reduction) as much as the effectiveness is enhanced by the improved adherence. Yet few CEA models have detailed how adherence should be incorporated into value assessment frameworks. When including adherence in value assessments, many studies rely on assumptions of perfect adherence or clinical trial adherence as a proxy which is not representative of real-world use patterns (van Onzenoort et al. 2011).

In practice, inclusion of treatment adherence in GCEA can be accomplished through changes in more traditional value dimensions including changes in effectiveness, costs, and utility. GCEA provides researchers with a series of key questions that help determine how adherence-improving factors can be included in value assessments (Box 8).

Once these questions are answered, a few methods exist to implement adherence into value assessments. If using a Markov model, adherence can easily be captured as patients transition during each cycle to an adherent or non-adherent state, with corresponding efficacy (improved health outcomes), costs (lower medical costs due to improved health), and utilities (less caregiver burden, higher GRA-QALYs from time spent in better health). One could also use pharmacokinetic/pharmacodynamic modelling to examine how suboptimal adherence is likely to impact real-world effectiveness (Shafrin et al. 2017). *Ex-post* value assessments can measure the true benefit to patients from adherence-improving factors, but rely on real-world

Box 8: Guiding questions for including adherence in value frameworks.

1. Does the proposed treatment have certain aspects that promote adherence compared to the standard of care?
2. If adherence improves, how will that impact treatment effectiveness relative to the efficacy measure in clinical trials?
3. If adherence improves, how will that impact treatment cost and medical cost offsets?
4. If adherence improves is there a quality-of-life impact outside of improved effectiveness?
   - For instance, long-acting monthly injectables may be more convenient than daily injections and thus, there may be a QoL impact outside of any change in effectiveness

data that are not readily available when value-based pricing decisions are made at drug launch.

6.4 Direct Non-medical Costs

As a consequence of their disease, many patients (and their families) incur direct non-medical costs to accommodate disability and diminished health-related quality of life. For example, parents of children with dyslexia often incur higher educational costs as tutors and other forms of remedial teaching become required to progress in school at the same rate as their peers. Other patients, such as those with amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Duchenne muscular dystrophy, and other diseases that impact ambulatory ability experience costs of retrofitting their homes with wheelchair ramps and arm railings.

Furthermore, while not included in conventional CEA pharmaceutical costs, patients incur additional travel costs in order to receive care such as medical evaluations, consultations, physical therapy, and infusions administered at an inpatient or outpatient facility. As demonstrated by Alzheimer's patients, these direct non-medical costs provide a substantial burden and a benefit of medical innovation is reductions in these costs.

However, direct non-medical costs are highly specific to each disease and no single method can be readily generalizable across indications. As a result, GCEA recommends researchers consider the potential direct non-medical costs for a disease of interest and include those costs in their model.

7 Discussion

As key healthcare decision-makers increasingly demand more robust and comprehensive value assessment frameworks and supporting methods, health economics

and outcomes research professionals (e.g. researchers, modelers, health economists, and value assessors) must not only understand but also be able to implement quantitative and qualitative approaches for comprehensively measuring societal costs and benefits for new medicines and other health technologies. Yet, finding a consistent and empirical path forward for the incorporation of the value components into value assessment approaches has been a challenge, with a lack of consensus on how particular elements of value can be estimated and concerns regarding their overlap in value assessment. As such, in this paper, we introduce GCEA as an ethos for discussing the value of innovation, lay out an inventory of its tools and methodologies, and offer a practical guide to incorporating a series of 15 distinct value sources.

We broadly classified these 15 values into the following four categories: (i) uncertainty resulting from disease and treatment (*outcome certainty*, *disease risk reduction*, and *value of knowing*), (ii) dynamics over time (*dynamic net health system costs*, *dynamic prevalence*, *option value*, *scientific spillover*, and *societal discount rate*), (iii) beneficiary impacted by treatment (*patient-centered health improvements*, *equity*, and *family and caregiver spillover*), and (iv) additional value components (*community spillover*, *productivity*, *adherence*, and direct medical and *direct non-medical costs*) (Table 1).

To ensure careful and systematic incorporation of these broader value components, our GCEA inventory is built upon eight key methodological advances from recent academic literature.

- First, gains in outcome certainty are captured by the GRA-QALY as computed within the GRACE framework (Lakdawalla and Phelps 2022). GRACE also includes the value of disease risk reduction and generates a more accurate willingness to pay by computing the RASA-WTP; the use of GRA-QALYs and RASA-WTP also allows for value assessments to consider patient-level characteristics, such as disability status and disease severity. Furthermore, the value of knowing can be readily measured and incorporated into value assessments from a variety of stated preference surveys (Phillips et al. 2006).
- Second, we recommend the incorporation of dynamic drug prices and disease prevalence to better align how changes in drug costs and incident patient population sizes affect value of treatment in the real world over time using stacked cohort models and dynamic inputs (Whittington et al. 2023).
- Third, to capture that more novel drugs can produce "scientific spillover" that inspire future drug innovations, GCEA provides recommendations for analyzing drug novelty and expected knowledge spillovers (Drupp et al. 2018; Frankel et al. 2023; Lanthier et al. 2013; Ramsey 1928; Young 2023).
- Fourth, following this drug innovation spillover, *ex ante* option value can be easily implemented to apportion the potential health benefits of future

innovations that patients are enabled to attain by taking novel, efficacious treatments available today (Li et al. 2022).
- Fifth, GCEA recommends researchers justify their selection of either the real risk-free interest rate or the use of the Ramsey equation when selecting a discount rate for costs and benefits (Drupp et al. 2018; Ramsey 1928; Young 2023).
- Sixth, societal preferences for reduced inequality can be incorporated into treatment value estimation through the use of DCEA (Love-Koh et al. 2019).
- Seventh, treatments can also generate broader value via "family and caregiver spillover" by improving caregivers' quality of life and reducing the productivity losses experienced by caregivers; through GCEA, relative improvements in caregivers' QALYs can be evaluated and added to the value generated from GRA-QALY gains of patients in GRACE, and expanded considerations of caregiver productivity costs are captured through the use of an augmented multiplier method (Chiu et al. 2022).
- Eighth and finally, we discuss how value assessments should consider additional value to patients and their communities by (a) estimating community spillovers, such as fewer business closures due to contagious disease; (b) quantifying patient productivity gains due to better management of disease, including the macroeconomic spillovers of a larger labor supply; (c) considering adherence improving factors which improve clinical outcomes in the real world; and (d) including cost savings generated from avoidance of direct non-medical costs of disease under the standard of care.

For anyone wondering when to conduct a GCEA versus a conventional CEA, we would suggest the following litmus test. Imagine that the upper limit of willingness to pay that is calculated by the assessment were communicated back through time to the inventors and investors considering whether to work on this innovation. If they were discouraged from pursuing the work by seeing how little their invention would be valued someday if they were even successful, would society be better off for having done that assessment in that way?

The stakes for correctly estimating the total value of treatments are high, especially when considering the case that patients may go without key treatments when innovation is disincentivized by value underestimation. Moreover, not paying for a seemingly high-priced drug that can go generic might only result in society spending more over time on hospitals, where costs largely only increase (i.e. there is no genericization mechanism for medical services). As such, we recommend researchers should review all sources of societal benefits and cost outlined in this paper – beyond conventional CEA – and determine the relevance and feasibility of incorporating them into an assessment.

7.1 Limitations

While GCEA presents a more comprehensive inventory for capturing novel and broader value of treatments, as with any work-in-progress framework, it does have several limitations. First of all, each element discussed in this paper provides its own, unique source of value to patients, but many cannot be valued in isolation and require the use of a broader unified framework to be incorporated into societal cost-effectiveness and value-based pricing decisions. For example, the values accounted for by the Outcome Certainty (the value of reducing uncertainty and the value of hope) and Disease Risk Reduction (the insurance value) petals are incorporated in a comprehensive manner using GRACE and cannot be valued in isolation for contextual purposes.

Furthermore, GCEA relies on a number of methodologies that themselves have limitations. For example:

- Although being required for GRACE to generate the most patient-centered results, estimates of patient risk aversion over disease-specific health outcomes are limited. DCEA is highly sensitive to the inequality aversion, however, literature on this is also relatively sparse (Li et al. 2019; Li et al. 2022). Besides these key parameters, many disease-specific estimates of community spillover, family and caregiver spillover, and adherence may have limited data available for incorporation into GCEA in practice. Additional data collection is required to accurately model GCEA.
- Quantitative approaches to estimate patient non-market productivity loss and translate drug novelty into treatment value itself due to scientific spillover have not yet been developed.
- Predicting the trajectory of branded drug prices and the magnitude by which drug prices fall after loss of exclusivity is uncertain and must be based on analogous treatments, competitive landscapes, and evolving regulatory environment.
- The GCEA equity petal, as currently constructed, focuses on reducing inequality in health outcomes. However, there are many other dimensions of inequality (e.g. income inequality) which also have value. Future work should consider if these other dimensions of inequality should be considered and, if so, how they can be integrated into the GCEA framework.

Conventional CEA, however, does not offer us a solution for all these limitations of GCEA. Rather, conventional CEA simply assumes a default value for every petal that it omits. By ignoring dynamics, for instance, conventional CEA assumes that a drug will *never* go generic. By ignoring productivity, it assumes that a patient and their

caregiver will not be more productive – or this productivity is valued by society at $0 – which is also an extreme assumption. Thus, while GCEA limitations are important to note, GCEA does mark a significant improvement over conventional CEA's simple but extreme assumptions surrounding the value of broader value elements.

Both conventional CEA and GCEA, while impressive to some for their quantitative precision, require humility in their interpretation precisely because of their limitations in capturing the revealed preferences of society and its many stakeholders. As the Second Panel on Cost Effectiveness and Health in Medicine states, "cost-effectiveness analysis is not by itself a sufficient decision-making standard and that it does not capture all relevant concerns."(Sanders et al. 2016a)

7.2 A Path Forward

Despite these limitations and areas for future research, this current guidance on GCEA aims to provide researchers with a variety of improved methodological approaches over the conventional cost-effectiveness framework, which quantitatively omits all but, on occasion, a handful of the GCEA value flower's petals. While the added value of many petals may be more challenging to calculate, this paper has extensively cited a growing body of research that has demonstrated that these values are real and should not be ignored. Indeed, the purpose of GCEA is to transition value assessment from the narrow payer perspective to incorporating real sources of value to our society that have been empirically measured in the literature.

In fact, GCEA's feasibility is highlighted as value assessment literature is already moving in this direction and some studies can be considered to have taken on different 'versions' of GCEA. For example, a study evaluating the net social benefits for treating all hepatitis C-infected individuals included the petals of scientific spillover, family and caregiver spillover, patient-centered health improvements, productivity, adherence, dynamic net health system costs, disease risk reduction, and the value of hope (Moreno et al. 2017). A study on a recent treatment for early Alzheimer's disease included the productivity and family and caregiver spillover petals (Whittington et al. 2022).

The limitations of GCEA are no reason for sticking with conventional CEA, which has far more limitations by the simple fact that it ignores – or assumes a value of 0 – for most of the petals of the flower. Even when a CEA doesn't take various petals into account, possibly due to lack of data, its own limitations section should acknowledge that these values are missing and point out that their inclusion would likely alter the ICER and maybe even the conclusion about a product's societal cost-

effectiveness. In countries that rely on CEA to set coverage decisions, the recognition that petals were omitted due to lack of data should spark discussion of whether to err on the side of coverage. CEAs can always be refined and decisions changed once there are more data, but if innovation is discouraged because CEAs undervalue it, there won't be anything to re-evaluate.

Countries that use CEAs to make decisions for their populations would ideally make sure that CEAs done for their narrow purposes are not written in a way that gives the impression that they are passing judgement on the value of a medicine for others. While it's not clear why any country would ignore a demonstrably real value, doing so for reasons that are country-specific should be accompanied with an acknowledgement that this value could be present for others and therefore the assessed technology could be worth more to others.

Despite the clear need for more broadly capturing treatment value, additional research is needed to convert the GCEA inventory of value elements into a formal value assessment framework. For instance, the GCEA approach outlined in this paper does not explicitly recommend a specific willingness-to-pay per GRA-QALY threshold, nor how the additional of each GCEA petals would impact this threshold. Additionally, this current guidance does not describe how to address issues of potential double-counting. For instance, if caregiver and productivity impacts are incorporated in the value assessment, should the willingness to pay per QALY change and if so, how? Additionally, if one calculates the option value of an initial treatment, should that impact the value assessment conducted of the subsequent therapy (Towse 2022)?

Some suggest that if CEA calculates that a drug is not cost-effective and GCEA's extra petals reduce the ICER below the cost-effectiveness threshold, then the threshold should be lowered. While this paper does not explicitly comment on the appropriate willingness to pay for health gains for different countries, GCEA should be seen as a series of methods to incorporate other forms of value that are well-recognized but currently unaccounted for in conventional CEA. Moreover, the more variables a GCEA includes, the wider the confidence interval of results. The range of possible answers should not be taken as a flaw with the approach but as a valuable warning not to assume that math can always substitute for the reveal preference of actual people. Whether one does conventional CEAs or GCEAs, the more one recognizes how much conventional CEAs have omitted what actually matters to people, the more humility one should have for what today's GCEAs may get wrong about what we will someday discover we've long valued. Even if GCEAs only serve as reminders to keep an open mind about all that we have still failed to account for and to not to just ignore what we can't compute, they will serve a useful purpose.

8 Conclusions

Our healthcare ecosystem comprises of diverse stakeholders that seeks to develop and deliver innovative health technologies to maximize the benefits to those in need of care while ensuring sustainability. Understanding the true value of health technologies in decision-making is crucial to ensure that treatments are being delivered efficiently while balancing the incentives for continued innovation of technologies that yield a consumer surplus. Value assessment approaches generate signals of the value of health technologies but can also help us understand the prices we see being paid in the market.

Sometimes market participants continue to pay more for a medicine than a conventional CEA would suggest is rational, and yet adding a few petals of the value flower can reveal that the market price is actually cost-effective. Especially when coverage decisions are based on CEAs, whether or not a CEA incorporates a value element may have a real impact on people's lives. It is therefore imperative that we update our approaches to valuing innovative health technologies with GCEA while acknowledging our continued inability to compute the value of all that we actually value.

To comprehensively capture the value of health technologies – both cost and benefits – novel and broader sources of value should be incorporated into cost-effectiveness frameworks. GCEA provides a unified, updated inventory of societal value components and recommends best practice guidance to empirically estimate the total value of medical innovation. This paper aims not only to enumerate and define these value components, but also to explain clearly how these can be estimated in practice. By using the GCEA to incorporate comprehensive societal costs and benefits, researchers and policy makers will be able to better appreciate the value that these medical technologies bring to society.

9 Note to the Reader

The term "generalized cost effectiveness analysis" or GCEA has been used in the past by the World Health Organization (WHO) (Murray et al. 2000). While the version of GCEA labelled in this paper does share similarities with the WHO's GCEA approach – including a focus on societal costs and benefits as well as addressing concerns around "prioritizing the sick, reducing inequalities in health, or addressing the well-being of future generations" (Edejer 2003), these two GCEA initiatives should be viewed as distinct, with different origins, objectives, and aspirations.

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a number of life science companies and professional associations that are interested in promoting a broader societal perspective on the economic value of medical technologies. Ricard Willke has no conflicts of interest to declare. Jason Shafrin is an employee of FTI Consulting, Inc., a consulting firm to health care, life sciences, government and non-government institutions. Charles Phelps reports personal fees from EntityRisk, personal fees from Institute for Value and Innovation (IVI), personal fees from Pfzer, and personal fees from No Patient Left Behind. Jalpa Doshi reported receiving personal fees from AbbVie, Acadia, Janssen, Merck, Otsuka, and Takeda; grants from Janssen Scientific Affairs, LLC, Merck and Spark Therapeutics, all unrelated to the submitted work. Jaehong Kim is an employee of FTI Consulting, Inc., a consulting firm to health care, life sciences, government and non-government institutions.

Appendix

Appendix Conceptual Example: Outcome Certainty

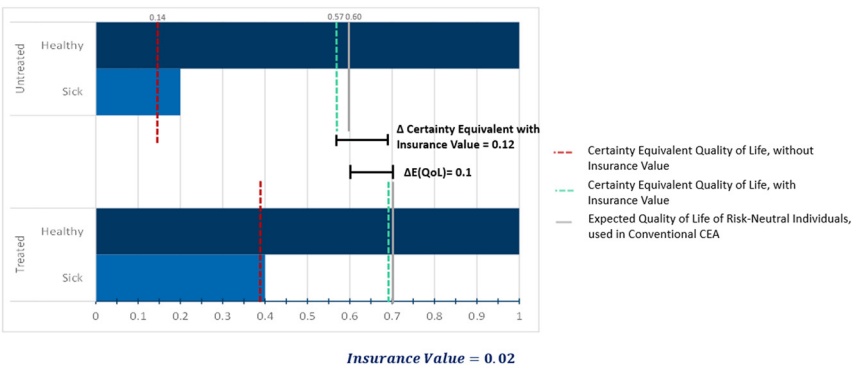
Consider an individual who is indifferent between receiving \$30 for certain and playing a coin-flipping game that awards \$100 for heads and a loss of \$20 for tails. Then, for that individual, the game's "certainty equivalent" value is only \$30 – even though the game's average outcome is \$40 (because $50\,\% \times -\$20 + 50\,\% \times \$100 = \$40$). The fact that the \$30 certainty equivalent is less than the average reflects the individual's aversion to the uncertain outcomes, paying \$20 or receiving \$100. In the same way, the decision to buy homeowners insurance (even if not required to do so by the terms of a mortgage) reflects the preference for a specified, certain, periodic premium over a (small) risk of a large loss – even though the insurance policy's premium exceeds the average cost of self-insuring against that low-probability loss.

While a simple example, the demonstrated preference to receive a certain monetary allocation, with certainty, is applicable to health allocations as well. Consider that instead of flipping a coin, a hypothetical patient with receives treatment once with two possible outcomes. As a result of treatment, the patient can have a QoL improvement of 0.2 with probability 50 % or a QoL improvement of 0.6 with probability 50 %. Suppose this patient is indifferent between this treatment and another, which offers a 0.3 QoL improvement 100 % of the time (i.e. with certainty), despite the expected value of the first treatment being higher ($0.6 \times 50\,\% + 50\,\% \times 0.2 = 0.4$). Similar to the \$30 monetary gain in the first example, the QoL gain of 0.3 represents certainty equivalent QoL value because it is the QoL allocation, with certainty, that awards the patient the same expected utility gain as taking the gamble.

Appendix Conceptual Example: Disease Risk Reduction

To better understand the concept of disease risk reduction consider Appendix Figure 1. Suppose for some disease, 50 % of the population will get sick (QoL_{sick} = 0.2) in the next period, and the remaining 50 % will remain perfectly healthy ($QoL_{healthy}$ = 1.0). Also assume that a new treatment is developed such that the symptoms of the disease are mitigated and sick patients who are treated have an improved quality of life ($QoL_{treated}$ = 0.4). There is no cost for simplicity. In the conventional CEA framework that only considers the risk-neutral patient only, the treatment value is simply 0.2 QALYs (=$QoL_{treated}$-QoL_{sick} = 0.4–0.2). However, from a healthy risk-neutral individual's perspective, the treatment value is estimated as 0.1 QALYs because the expected quality of life is 0.7 (=50 % × $QoL_{treated}$ + 50 % × $QoL_{healthy}$ = 50 %*0.4 + 50 %*1.0) when treated and 0.6 (=50 % × QoL_{sick} + 50 % × $QoL_{healthy}$ = 50 %*0.2 + 50 %*1.0) when sick.

The value under the conventional CEA framework is obtained again by setting the percent of the sick people to 100 %. Now, assume that healthy individuals are risk-averse and that the certainty equivalent quality of life when considering the expected value of the treatment outcomes only is 0.14 without treatment (CE_{sick}) and 0.38 with the treatment ($CE_{treated}$). Observe that due to risk-aversion and outcome uncertainty, both certainty equivalents are lower than their corresponding quality of life, QoL_{sick} = 0.2 and $QoL_{treated}$ = 0.4 (Figure 4). Then, for a healthy risk-averse individual, the expectation of the certainty equivalent quality of life when treated is 0.69 (=50 % × $CE_{treated}$ + 50 % × $CE_{healthy}$ = 50 %*0.38 + 50 %*1.0) and 0.57 (=50 % × CE_{sick} + 50 % × $CE_{healthy}$ = 50 %*0.14 + 50 %*1.0) when sick, yielding a treatment value of 0.12 QALYs. In other words, the additional incremental value above and beyond the mean value of health gains to risk-averse individuals – 0.02 (=0.12–0.10) – is known as insurance value. This insurance value was created because the new health technology shrunk the variance between the health states in the "healthy" and "sick" conditions.



Appendix Figure 1: Conceptual example of insurance value.

Appendix Numerical Example: Option Value

Ex-Ante Option Value

Recall from Box 3 in the Option Value petal section that *ex ante* option value can be computed according to four steps: forecasting the timing of future innovation, estimating the potential health benefits and costs of the future innovation, forecasting the probability of approval and uptake rate in the future, and calculating the increase in net monetary benefit due to option value for the initial treatment innovation. The following numerical example provides an overview of the steps required to calculate *ex ante* option value following a published model from Li et al. (2019). (Li et al. 2019) that evaluate the option value of ipilimumab for patients with metastatic melanoma. The first three steps of computing real option value are included in Appendix Table 1.

In the first step, researchers calculated that the next innovative systemic therapy for metastatic melanoma would arrive seven months after the model start year, based upon data from phase III clinical trials registered on clinicaltrials.gov. Second, the same clinical trial data was used to model a median overall survival (expected efficacy) of 13 months while another model published in the literature was used to predict the pricing of future cancer innovations. Third, data from the FDA and clinicaltrials.gov was used to inform the probability of approval and uptake rate (percent of patients on progressive disease initiating new 2 L drug).

Appendix Table 2 provides the results of calculating the net monetary benefit of *ex ante* option value. The inclusion of option value resulted in 0.42 additional QALYs per patient[9] for the treatment group (an additional 0.06 incremental QALYs) and additional treatment costs. Overall, the ICER decreased when option value was considered.

Appendix Table 1: Parameter estimation for ex-ante option value (Li et al. 2019).

GCEA recommended step (Box 3)	Parameter	Estimate
1	Months until innovation arrival	7 months
2	Overall survival on new 2 L drug	13 months
	Cost per treatment course for new 2 L drug	$1,40,617
3	Probability of approval	77 %
	Percent of patients on progressive disease initiating new 2 L drug	60 %

9 Within GCEA, QALY's per patient would be replaced with GRA-QALYs to account for Patient-Centered Health Improvements.

Appendix Table 2: Treatment value with option value (Li et al. 2019).

GCEA recommended step	Outcome	Without option value (CEA result)			With option value		
		QALY gained	Cancer cost	Healthcare cost	ΔQALY gained	ΔCancer cost	ΔHealthcare cost
4	Ipilimumab + dacarbazine	2.71	$3,56,921.00	$3,68,466.00	0.42	$81,733.00	$83,650.00
	Dacarbazine	1.98	$1,72,991.00	$1,81,010.00	0.36	$69,625.00	$71,281.00
	Incremental	0.82	$1,83,930.00	$1,87,456.00	0.06	$12,108.00	$12,369.00
	ICER, $/QALY		$2,23,964.00	$2,28,258.00		$(937.00)	$(917.00)

Ex-Post Option Value

As discussed in Option Value section, researchers may also calculate option value *ex-post*, which while a more robust research method providing less variability in it estimates is not useful at drug launch. Appendix Table 3 details how option value is calculated from an *ex-post* when the approval of the innovative treatment is certain at a given time and the uptake rate, efficacy, and costs are determined by retrospective cohort analyses. This example comes from a paper by (Wong et al. 2021) and you can review that paper for more details.

Appendix Numerical Example: Distributional Cost Effectiveness Analysis (DCEA)

Recall from Box 6 in the Equity petal section that implementing DCEA follows six steps: selection of subgroups, measuring costs and benefits of treatment, calculating incremental net health benefit by group, estimating QALEs, calculating EDE QALYs, and using EDE QALYs to measure value. The following numerical example overviews the steps required to implement DCEA into value assessments following a published model examining the health equity impacts of smoking cessation withing the United Kingdom's healthcare system as published in (Yang et al. 2020). An overview of the methodology and results of the study are summarized in Appendix Table 4.

The authors selected subgroups who experience health disparities following the Index of Multiple Deprivation (IMD) which measures socioeconomic disparities through a collection of socioeconomic factors. Selection of the groups to be analyzed is step 1 of the DCEA procedure. Higher IMD quintiles were viewed as the least "at risk" and lower quintiles were viewed as "most at risk" due to socioeconomic factors. Following the second step of implementing DCEA, the costs and benefits of smoking cessation were derived from a conventional CEA model for each IMD subgroup. Third, the net health benefit per subgroup was calculated using literature on population size and each subgroup's opportunity costs of receiving care as well as the conventional CEA results. The opportunity costs borne by different IMD quintiles are subtracted from the incremental direct health benefits, by subgroup, observed in the conventional CEA model. Health opportunity costs were defined as the other forms of care foregone in order to devote resources to smoking cessation programs. The incremental net health benefit (iNHB) per individual was simply the sup-population net health benefit divided by the number of people within that sub-population and represents the health benefit accrued to eligible patients (i.e. IMD1 individuals who smoke) equally distributed across all subgroup members in the general population. Next, the distribution of health outcomes was computed by adding each sub-group's incremental net health benefit to baseline QALE's which were estimated in the

Appendix Table 3: Ex-post option value (Wong et al. 2021).

Outcome	First-line ipilimumab		Second-line ipilimumab	
	No subsequent CIT	Subsequent CIT	No subsequent CIT	Subsequent CIT
Proportion of patients in each cohort	78 %	22 %	81 %	19 %
Mean overall survival, months	21.7	38.3	13.9	38.9
Option Value (survival, months)	22.4 % × (38.3 − 21.7) = 3.7		19.1 % × (38.9 − 13.9) = 4.8	
Percent of conventional survival gain	3.7/(21.7 − 11.1) × 100 = 34.9 %		4.8/(13.9 − 5.4) × 100 = 56.5 %	
Proportion of patients receiving first-line/second-line ipilimumab, %	77.4		22.6	
Overall option value	3.9 months			

Appendix Table 4: Results of smoking cessation DCEA, adapted from Yang et al. 2020).

GCEA recommended step (Box 6)	Methods			Result, by Subgroup					Total
		Value	Sources and equations	IMD1 (most deprived)	IMD2	IMD3	IMD4	IMD5 (most deprived)	
Step 2	(a)	Incremental Direct health benefits	*CEA model result*	6,560	15,619	13,201	19,350	18,233	
	(b)	Incremental Costs	*CEA model result*	−1,25,44,948	−3,25,07,852	−2,90,16,052	−4,29,24,171	−3,93,98,949	
	(c)	Total incremental costs	*Sum of (b)*						−15,63,91,946
Step 3	(d)	Total opportunity costs	*(c)/£20,000 per QALY*						−7,820
	(e)	Proportion of health opportunity costs	*Love-Koh et al. (2020)*	0.260	0.220	0.220	0.160	0.140	
	(f)	Health opportunity costs, QALYs	*(d) × (e)*	−2,033	−1,720	−1,720	−1,251	−1,095	
	(g)	Incremental NHB, QALYs	*(a) − (f)*	8,593	17,339	14,921	20,601	19,328	
	(h)	Population size	*Office for National Statistics, (2017)*	83,07,456	88,63,275	87,90,681	86,57,257	83,76,275	
	(i)	Individual iNHB, QALYs	*(g)/(h)*	0.0010	0.0020	0.0017	0.0024	0.0023	
Step 4	(j)	Baseline QALE (no intervention)	*Love-Koh et al. (2015)*	64.7000	68.5000	70.6000	73.6000	75.6000	
	(k)	QALE with e-cigarette	*(i) + (j)*	64.7010	68.5020	70.6017	73.6024	75.6023	
Step 5	(l)	Baseline EDE, QALYs							69.47
	(m)	EDE with intervention, QALYs							69.48
Step 6	(n)	Population iEDE	*((m) × Sum of (h)) − ((l) × Sum of (h))*						70,002
	(o)	Impact on overall health	*Sum of (g)*						80,782
	(p)	Impact on health inequality	*(n) − (o)*						−10,780

£20,000 per QALY is the assumed willingness to pay for a QALY in England. Love-Koh et al. (2015) provides estimates of the social distribution of health in England, the setting of the study.

literature. Fifth, EDE QALYs were computed by utilizing an Atkinson social welfare function with an inequality aversion parameter value ε of 10.95. Recall that the form of the Atkinson social welfare function is that the EDE QALYs are defined as follows:

$$\text{EDE} = \left(\frac{1}{N}\Sigma h_i^{1-\varepsilon}\right)^{\frac{1}{1-\varepsilon}}$$

Where EDE represents the EDE QALY, N represents the total population size, h_i is the subgroup QALE for those receiving the iNHB of the intervention as well as those who do not receive the intervention, and ε is the inequality aversion index. The resulting population incremental EDE QALYs are defined as the product of EDE QALYs of the intervention group, the difference between subgroup population and their EDE QALEs, and the total population (sum of all subgroup populations). As demonstrated by row (o) of the table, the inclusion of reduced health disparities generates an additional £10,780.[10]

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10 In the table, additional value due to equity is negative because the author's calculation subtracted the societal health gains from the incremental EDE QALY gains.

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