GENERALIZED COST-EFFECTIVENESS ANALYSIS WITH DYNAMIC PREVALENCE FOR IMPROVING HEALTH EQUITY AMONG RARE DISEASES

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ABSTRACT

There is a documented link related to known relative risk preferences in health and willingness-to-pay (WTP) using generalized risk-adjusted cost-effectiveness (GRACE) theory for the valuation of health technology. As a result, GRACE addresses limitations of cost-effectiveness analysis pertaining to biases against patients with disabilities, among other health equity concerns. Notwithstanding, the rarity of a disease further exacerbates inequitable patient access to healthcare, as decisionmakers are often persuaded to allocate healthcare resources to larger subgroups, all else being equal under fixed WTP. This paper examines the relationship between relative risk in GRACE theory to relative risk in epidemiologic foundations in order to establish a correlation between WTP and the prevalence of disease. The analysis suggests that WTP increases exponentially as diseases become rarer based on the standardized prevalence factor using a Box-Cox transformation of prevalence. As a result, this approach offers a solution to empirical incorporation of the rarity of disease with dynamic prevalence over time in cost-effectiveness analysis in addition to other novel value elements established in GRACE theory, namely health equity, disease severity, insurance value, and value of hope. This approach to generalized cost-effectiveness analysis suggests a method by which dynamic prevalence may help inform priorities for resource allocation across rare disease cohorts.

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1. Introduction

Cost-effectiveness analysis (CEA) is a convenient tool for estimating value in the conduct of health technology assessment. CEA can be used to estimate the degree of opportunity costs in medical decision-making by comparing incremental results to a willingness-to-pay (WTP) threshold (Garber & Phelps, 1997). If CEA results exceed the threshold, then decisionmakers are willingly accepting that opportunity costs may exceed the value of a technology based on a societal WTP. For example, the WTP for the U.S. Medicare program is approximately $104,000 per quality-adjusted life year (QALY) using an opportunity cost framework (Vanness et al., 2021).

These thresholds facilitate decision-making across health technologies and across cohorts. A decisionmaker strongly considering adding a novel, high-cost technology to a medical formulary despite prior knowledge that the incremental cost-effectiveness ratio exceeds an established threshold may be willing to accept immediate opportunity costs (Brekke et al., 2023). The overall goal of the decisionmaker may then entail prioritizing other health technologies on a formulary that are below the WTP threshold in order to balance out opportunity costs across technologies for a range of health conditions.

Recently, innovations in health technology, ranging from curative direct-acting agents for hepatitis C virus to cell and gene therapies for rare conditions (e.g. sickle cell disease, haemophilia) have presented economic challenges to decisionmakers (Basu et al., 2024; Garrison et al., 2021). These classes of technology, although borderline cost-effective using conventional methods, may have exceeded budget constraints that make their addition to a drug formulary cost-prohibitive for most covered beneficiaries in a risk pool. These coverage decisions have resulted in alternative payment models such as “cost

sharing" and "warehousing" in order ensure that patients with more severe symptoms or disability have priority access to novel health technologies without depleting decisionmakers' budgetary resources of an entire risk pool facing multiple priorities (Karmarkar et al., 2022; Padula et al., 2021).

Recently, conventional CEA has come under scrutiny because of its limitations, in particular, biases against patients with disabilities, underrepresented minorities and patients with rare diseases. The International Society of Pharmacoeconomics & Outcomes Research (ISPOR) put forth a set of novel value elements (Lakdawalla et al., 2018) to address these limitations methodologically through the conduct of generalized CEA in order to directly adjust CEA parameters and the WTP threshold for concerns related to disability, health equity, rarity of disease, etc. (Padula & Kolchinsky, 2024). While these novel value elements present important adjustments to CEA in theory, the field has a limited number of established methods based on economic theory to control for them in generalized CEA.

Lakdawalla & Phelps presented the generalized risk-adjusted cost-effectiveness (GRACE) approach as a method to simultaneously control for several novel value elements (i.e. disease severity, value of hope, insurance value, and health equity) when applying adjustments to the WTP threshold and health utility in order to incorporate diminishing returns to health in the creation of utility (Lakdawalla & Phelps, 2021). This method presented an initial theoretical effort to advance generalized CEA to better incorporate concerns around health equity and disability beyond the structural adjustments introduced in distributional CEA (Griffin et al., 2020).

Since the introduction of GRACE, Ramagopalan and colleagues (2024) have expanded the proposed range of novel value elements to also include dynamic prevalence, which represents considerations about changes in the size of a patient cohort over time, and the potential that opportunity costs could shift as cohorts become more or less rare at fixed value and cost of treatment. Dynamic prevalence represents a critical novel value element in the consideration of health equity, especially given that some rare diseases are isolated in minority populations, such as sickle cell disease among patients who are mostly of African ancestry or identify as Black.

The recent development of cell and gene therapies for conditions such as sickle cell disease at a list price of approximately $1 million to $3 million per course of treatment represents remarkable opportunity to eliminate a painful (Goshua et al., 2023), debilitating chronic condition from a minority population that has often been disenfranchised from access to healthcare for other needs (Attonito et al., 2021). While these therapies for sickle cell disease have been found cost-effective in certain scenarios, there uptake in the patient population has been slow given decisionmakers' apprehension to spend above budget constraints for a single cohort, or introduce additional opportunity costs (Basu et al., 2024). However, payers already spend much more for other single cohorts. For example, U.S. Medicare spends over $58 billion on the top-fifteen prescription drugs primarily indicated to treat a range of cancers, autoimmune conditions, diabetes, and cardiovascular conditions including: $10 billion on statins for the U.S. cohort of patients with hypercholesteremia (Sumarsono et al., 2021), over $13 billion on insulin for patients with diabetes (Cubanski, 2019), and over $18 billion on anticoagulants for patients with

atrial fibrillation (Troy & Anderson, 2021). It would cost approximately $10.4 billion to treat 20% of sickle cell disease cases with gene therapy in the U.S. Medicaid program today, assuming a list price of $1 million per course of treatment (Speller, 2023). Why would U.S. societal preferences deem hypercholesterolemia, atrial fibrillation, or diabetes higher priority to treat than curing sickle cell disease if the decision between these opportunities involves entirely eliminating the latter rare condition within a 5-year period, whereas the former conditions will all require continual chronic maintenance? These societal preferences underscore the mathematical impossibility of maximizing the utility of competing interests, needs, or wants as a result.

According to the philosophy of dynamic prevalence, WTP could shift to present a higher tolerance to opportunity costs for rare conditions than common conditions, thereby extending equitable access to favorable coverage decisions for smaller patient populations. We examine the theoretical foundations of extending generalized CEA with GRACE components to including dynamic prevalence in health equity, and furthermore provide a sample of WTP thresholds for a set of common and rare diseases based on previous trends in spending on health technology at the threshold for a number of conditions of known epidemiology (i.e. incidence or prevalence).

2. Theoretical Development

2.1 *Reviewing the foundations of cost-effectiveness analysis*

We begin with the widely accepted opportunity cost framework for cost-effectiveness analysis (Garber & Phelps, 1997), whereby a change in consumption of a

health technology (Δ ***C***) for incremental gains in utility over health (Δ $\boldsymbol{U_H}$) occur at or below an established societal WTP threshold (***K***):

$$K \geq \frac{\Delta C}{\Delta U_H} \quad (1)$$

We assume that costs are expended to shift health utility from a baseline value at *time* = 0, H_0, to a preferred health utility value in a subsequent timepoint (e.g. 1.0 QALYs). In doing so, healthcare expenditures may remain non-zero, but transition from an investment state of 'getting better' or 'getting well' (***U'***) to a preferred health state of 'staying well' (***U***) (Pronovost et al., 2021):

$$K \equiv \frac{U(H_1)}{U'(H_0)}\left(\frac{1}{H_0}\right) \quad (2)$$

Garber and Phelps concluded that the ratio of utility in these baseline and optimal states in (2), that is *U/U',* can be specified if relative risk aversion is known, under conditions of constant absolute risk aversion (CARA) for utility over consumption. That is,

$$U = \beta(1 - e^{-\gamma^Y}) \quad (3)$$

and

$$U' = \gamma\beta e^{-\gamma^Y} \quad (4)$$

and

$$U'' = -\gamma^2\beta e^{-\gamma^Y} \quad (5)$$

Garber and Phelps represent absolute risk aversion as a function of utility over consumption (i.e. $\mathrm{r} = \text{-U''/U'} = \gamma$) as well as the ratio of relative risk aversion (i.e. $r^* = \gamma^Y$).

These functions establish a relationship between risk aversion and shifts in utility over health, as calculated by Mulligan and colleagues (2024):

$$r^* = -\frac{U''}{U'}H \tag{6}$$

This understanding of relative risk aversion can be used to express how preferences shift under hyperbolic absolute risk aversion (HARA) utility in exchange for cash depending on the gross domestic product (GDP) per capita (***M***) relative to the WTP threshold (Phelps & Cinatl, 2021):

$$\frac{K}{M} = \frac{(1-\gamma)}{\gamma}\left(\frac{1}{r^*}\right) \tag{7}$$

In addition, other higher-order functions of utility over health exist for additional risk preferences, for example, relative risk prudence, $\boldsymbol{\pi^*}$, and relative risk temperance, $\boldsymbol{\tau^*}$:

$$\boldsymbol{\pi}^* = -\frac{U'}{U''}H \tag{8}$$

$$\tau^* = -\frac{U''}{U'''}H \tag{9}$$

These risk preference terms simplify Phelps and Cinatl's expression in *Eq. 7*. For instance, with the inclusion of relative risk aversion and relative risk prudence we obtain:

$$\frac{K}{M} = \frac{1}{\pi^* - 2r^*} \tag{10}$$

Under the circumstances where HARA utility has constant relative risk aversion (CRRA) with increasing utility, which is a critical constant to assume in generalized dynamic prevalence estimation, then the ratio ***K/M*** simplifies according to the established relationship between relative risk aversion and relative risk prudence (Noussair et al., 2014):

$$\pi^* = r^* + 1 \tag{11}$$

Thus,

$$\frac{K}{M} = \frac{1}{(r^*+1)-2r^*} = \frac{1}{1-r^*} \tag{12}$$

2.2 *Reviewing the foundations of relative risk in epidemiology*

The theoretical foundations of epidemiology prescribe that relative risk to health (***R***) is a function of exposure to disease and subsequent events that result in disease and increases in morbidity (Rothman, 2008), as expressed by the following equation:

$$R = \frac{A(C+D)}{C(A+B)} \tag{13}$$

Where,

- ***A***: Event in the exposed population;
- ***B***: No event in the exposed population;
- ***C***: Event in the unexposed population (i.e. "placebo effect");
- ***D***: No event in the unexposed population.

With increasing rarity of disease, this expression of ***R*** simplifies to an expression of the odds ratio (***OR***) in the following form (Gnardellis et al., 2022), since $1 - p_1 \approx 1$ and $1 - p_0 \approx 1$:

$$R \approx OR = \frac{A*D}{B*C} \tag{14}$$

Where,

$$\frac{A*D}{B*C} = \frac{\left(\frac{P_1}{1-P_1}\right)}{\left(\frac{P_0}{1-P}\right)} \tag{15}$$

R can be expressed as a function of ***OR*** and the incidence proportions of outcomes among the exposed (***P_1***) and unexposed (***P_0***), which leads to a new expression for ***R*** *(Zhang & Yu, 1998)*:

$$R = \left(\frac{A*D}{B*C}\right) / \left[(1 - P_0) + \frac{P_0*A*D}{B*C}\right] \quad (16)$$

Which according to Mantel-Haenszel direct standardization (Woolson & Bean, 1982), ***R*** *as an expression of* ***P_1*** *and* ***P_0*** can be simplified to:

$$R = \left(\frac{P_1}{P_0}\right) \quad (17)$$

We can further assume that ***$P_1 = (A+C)^2$*** *and* ***$P_0 = (A+B+C+D)^2$***. Given the fundamental epidemiological understanding that ***Prevalence*** = ***(A+C)/(A+B+C+D)***, then ***$R = (A+C)^2/(A+B+C+D)^2$*** (i.e. ***Prevalence***^{2}), if ***$(A+C)^2 = A*D$***. In a rare genetic disease where ***C*** automatically is equal to *zero*, then this equation is simply ***$A^2 = A*D$***. This is a reasonable assumption given that this equivalence emphasizes the rarity of disease in the exposed population relative to the unexposed.

2.3 *Linking definitions of relative risk in epidemiology to health economics*

In epidemiology, relative risk is a function of health and longevity, not consumption. In addition, relative risk to health is not itself relative risk-aversion. Relative risk aversion is the tendency to avoid uncertain risk and choose more certain, less beneficial ones (Oussedik et al., 2017). Relative risk aversion is a property of preferences alone, not the environment. However, in an environment where prevalence is high (p^S), people who are more risk averse are more likely to engage in transmissive behavior (i.e. reduced risk aversion, or preferences independent of risk) because the certainty of disease contraction becomes more attractive than uncertain payoffs of protective behavior (Matthies &

Toxvaerd, 2022). Conversely, rare diseases are not highly prevalent and generally more severe (p^R), and therefore relative risk aversion should remain constant (i.e. CRRA). Given shifts in relative risk aversion with the environment, changes in the environment should have a propotional impact on utility over health. Matthies and Toxvaerd establish this relationship between environment and relative risk aversion mathematically as:

$$E[U^R] = (1 - p^R)u(x_H^R) + p^R u(x_I^R) \quad (17)$$

and

$$E[U^S] = (1 - p^S)u(x_H^S) + p^S u(x_I^S) \quad (18)$$

Where, expected utility is differentiated by *R,* denoting a high *risk* infectious environment, or *S* to denote a *safe* environment. Furthermore, *p* is a function of relative risk, *R, that is:*

$$p^R = p + (1 - p)R \quad (19)$$

and,

$$p^S = p \quad (20)$$

Thus, concluding a direct relationship between *R* and *r* over health* given that $E[U] = f(r^*)$ (Mulligan et al., 2024).

In addition, there is a body of work establishing interactions between relative risks to health in epidemiology and the economics of health behaviors (i.e. relative risk aversion). For instance, Philipson (1999) determined that disease prevalence predicts behavioral response, and Dangerfield and colleagues (2022) further established that economic behaviors affect health risks. Therefore, the transitive property of equality links relative risk as a function of disease prevalence in epidemiology to WTP as a function of relative risk in economics since these interactions refer to the likelihood or the quantifiable

degree of uncertainty of an event occurring during a specific period of time (Arthur, 1981; Bhopal, 2016). Linking relative risk to *Eq. 10* as established by Lakdawalla and Phelps, we can conclude that HARA under CRRA results in a WTP expression that is inherently linked to population incidence *risk*, or prevalence - if removing the dimension of time – where *Risk* = *prevalence*:

$$\frac{K}{M} = \frac{1}{1-(Risk)^2} = \frac{1}{1-(Prevalence^2)^2} \quad (21)$$

3. Expected Utility Theory in Formulation of Thresholds of Opportunity Costs

Willingness-to-pay thresholds in healthcare are defined as the "estimate of what a consumer of health care might be prepared to pay for the health benefit", i.e. the monetary cost to achieve a (health-related) utility (Bertram et al., 2016). Currently, WTP thresholds could be considered as disease-blind, since they are commonly used as explicit criteria for coverage decisions for healthcare technologies (McDougall et al., 2020).

Disease-blind WTP thresholds are fundamentally flawed given the centralized nature of the decision of coverage by healthcare payers. Under the auspices of disease-blind WTP thresholds, decision-makers attempt to achieve the greatest possible (health-related) good, for the greatest possible number (of patients). Effectively, it is mathematically impossible to maximize the utility of two or more groups of healthcare consumers (von Neumann et al., 1944). Coverage decisions in healthcare are then misconstrued by applying disease-blind WTP thresholds to a covered population given that they risk transforming the maximization of health-related utility in a zero-sum game, that in order to provide resources for the most people, others in the minority, such as patients with

rarer conditions are left with fewer resources (Castanon et al., 2024; Garg, 2020; Verweij & Dawson, 2019).

Additionally, in the present example, we prefer using the term "covered population" instead of general population to be perspective agnostic. Therefore, the term is applicable to a population participating in a social economy that is exclusively financed by taxpayers, or those participating in a social-exchange economy covered by a commercial insurance entity. The budget holder – public or private – would still be forced by the illogical nature of maximization of health-related utility for the majority of the individuals. Furthermore, as the number of beneficiaries in a covered population increases, the rational approach is to maximize the utility of those in greatest numbers (Meltzer, 2001). Patients whose desired utility do not align with those in the majority are inexorably unaccounted for (i.e. "in a zone of indeterminateness") (von Neumann et al., 1944).

The expected utility theory provides a potential solution for overcoming the limitation of maximizing different or otherwise competing utility functions. Decision-makers could define health-related utility as the measure of objective *betterness or worseness* (Broome, 1991). Accordingly, the only function to be maximized is the utility of a covered population that trends towards 1.0 QALYs (i.e. achieving perfect health-related utility as a function of cost, *C*):

$$\lim_{C \to \infty} E[U(health)] = 1 \tag{22}$$

Where,

- ***E[U]***: Expected Utility
- ***C***: Cost of healthcare consumption

According to the foundations of the expected utility theory, the perfect health-related utility derived from consumption *c* of healthcare resources would correspond to the sum of each utility derived from each health-state that could affect a treated population, as defined by:

$$\mathrm{U(c)}E[W(health)] = 1 \iff 1 = \sum_{d \in D} P(d).W(d) \qquad (23)$$

Where,

- ***d***: a single disease
- ***D***: the set of all diseases affecting a covered population
- ***P***: Risk of disease *d* in covered population
- ***W***: utility of disease *d*

Consequently, the WTP thresholds for healthcare related consumption for maximizing the HARA under CRRA utility of a covered population will be weighed by the probability of each disease (*d)*, will be determined by:

$$K(U) = \sum_{d \in D} P(d).k(d) \qquad (24)$$

Where,

- ***k***: total WTP in healthcare
- ***K***: WTP for disease *d*
- **U:** Utility over consumption of healthcare

While recognizing the theoretical difference between utility over consumption over health-related utility, practically, the decision to allocate (the majority) of resources to pay for healthcare is not within the patient's decision making. Evidence from the CMS' National Health Expenditures Data shows that individuals (i.e. households) are only responsible for

28% of the total health spending (Centers for Medicare & Medicaid Services, 2022). Additionally, the allocation of resources for healthcare assumes that the covered population (via public or private insurance) will consume the expected resources for improving health status, rendering the proportion of patients untreated for the same condition irrelevant for the decision for resource allocation. Therefore, the utility derived from consumption was considered equivalent to the utility derived from health under the auspices of the Expected Utility Theory. This means that a decision to forego treatment by a patient is either in direct contradiction of the assumption of who finances healthcare or in direct contradiction of risk seeking behavior by individuals with the lowest levels of health (Mulligan et al., 2024). In conclusion, the allocation of resources for a covered population will require different disease-specific willingness to pay thresholds based on the risk of each disease (*d*), as demonstrated in *Eq. 21*.

4. Application of disease-specific willingness-to-pay thresholds

WTP threshold adjustment according to the effects of dynamic prevalence can be performed irrespective of the interpretation of the value of a statistical life (VSL). Prior authors have demonstrated the discrepancy between WTP thresholds based on gross-domestic product and VSL (Woods et al., 2016). Consequently, the approach proposed here utilizes WTP based on actual opportunity costs obtained by Vanness and colleagues (i.e. mean value of $104,000 per QALY) for the most prevalent observed conditions in the U.S. as a singularity (Vanness et al., 2021).

Using the 2021 medical conditions file from the Medical Expenditure Panel Survey (MEPS) (Agency for Healthcare Research and Quality, 2023), we estimated the frequency (i.e. prevalence) of each medical diagnosis as informed by the International Classification of Diseases, 10th Revision (ICD-10) code (**Figure 1**). Standardization was achieved via a Box-Cox transformation of the prevalence values, using the appropriate linear transformation (National Institute of Standards and Technology).

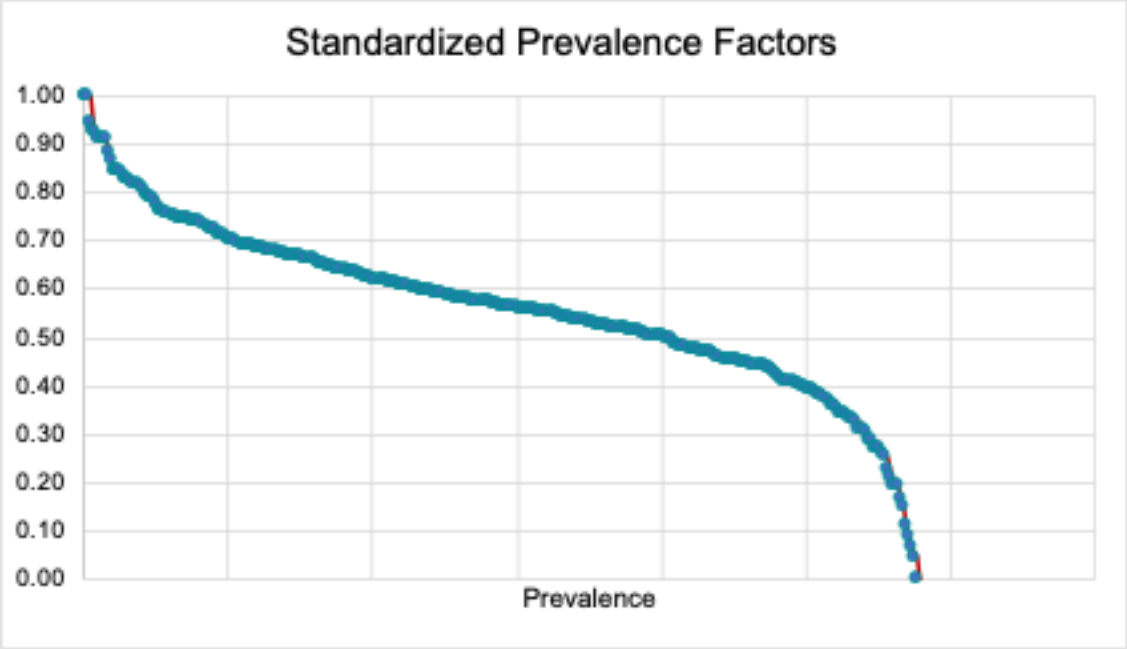


Figure 1. Standardized Prevalence Factors of Common Conditions in the U.S. Medical Expenditure Panel Survey**.**

Transformed values of prevalence were then implemented using *Eq. 21*, yielding a curve of WTP over prevalence of disease (**Figure 2**). In summary, WTP thresholds in the U.S.

could vary between $104,000/QALY for the most prevalent *observed* conditions and $990,049/QALY for the rarest observed medical conditions.

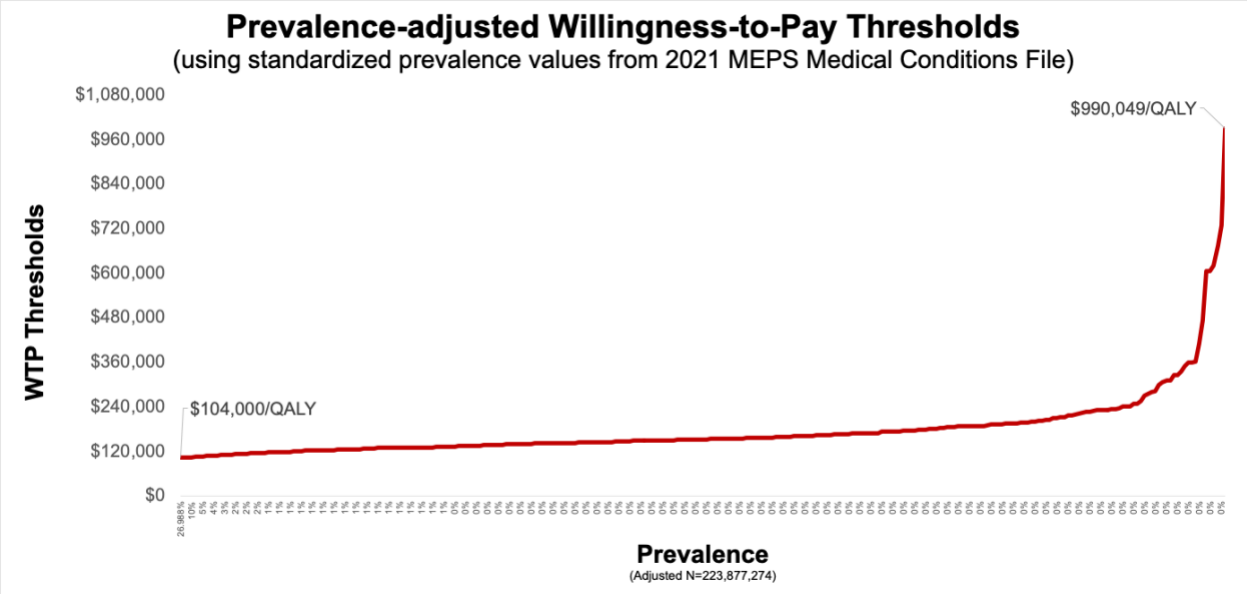


Figure 1. Prevalence-adjusted WTP threshold estimated using standardized values of prevalence from the 2021 MEPS Medical Conditions File.

To further illustrate the implications of this approach, an example for three conditions is provided below for:

- Hypercholesterolemia (ICD-10 E78.x): the most prevalent condition observed in the U.S. with 102 million cases (Carroll et al., 2017; Global Burden of Cardiovascular Diseases et al., 2018)
- Sickle Cell Disease (ICD-10 D57.x): a rare condition affecting 1 in 3,300 people in the U.S., or about 100,000 cases (Centers for Disease Control and Prevention, 2020)

- Duchenne Muscular Dystrophy (G71.01: an rare condition affecting 1 in every 6,500 people.(National Center for Advancing Translational Sciences)

As a result of *Eq. 21*, the prevalence-adjusted WTP threshold shifts between each of these conditions (**Table 1**).

Table 1. Prevalence-adjusted WTP Thresholds of select common and rare conditions.

Medication Condition	Prevalence	Adjustment Factor	Estimated WTP Threshold
Hypercholesterolemia	26.99% (MEPS data)	0	$104,000/QALY
Sickle Cell Disease	0.03% (Centers for Disease Control and Prevention, 2020)	0.825	$326,233/QALY
Duchenne Muscular Dystrophy	0.015% (National Center for Advancing Translational Sciences)	0.912	$621,247/QALY

5. Discussion

The first point to note is that the most common condition, hypercholesterolemia, has a substantial WTP threshold at $104,000/QALY. This is commonly accepted in the U.S. medical decision-making literature given the high cost of untreated hypercholesterolemia. Hypercholesterolemia is a precursor of diabetes mellitus and disease sequelae, including but not limited to lower-extremity diabetic ulcers, retinopathy, neuropathy, amputation, kidney failure, stroke, and cardiovascular disease. Thus, treatment for

hypercholesterolemia, usually with statins, represents a preventive measure against diabetes and is therefore avoiding downstream opportunity costs. The WTP fairly balances the likelihood of downstream consequences with budget impact for treating over 100 million in the U.S. with the condition at any given time.

The second point to note is that the two other conditions in the examples, sickle cell disease and Duchenne Muscular Dystrophy experience exponential gain in WTP given their increasing rarity in the U.S. population. This in turn increases their standardized prevalence factor closer to 1.0.

The third point to note is the translation of WTP threshold into budget impact. While *Eq. 21* allows for more expensive medicines to be covered for rarer conditions, the budget impact is traded off with increasing rarity. For example, potentially curative gene therapy for a condition such as sickle cell disease could cost $2-3 million per patient. Paying for 20% of the prevalent U.S. population (i.e. N = 100,000) in one year with this condition would cost up to $60 billion. Within 5 years, the burden associated with sickle cell disease would be largely contained or eliminated. By contrast, at a list price of about $1,500 per year, generic atorvastatin to treat hypercholesterolemia for 100 million individuals would cost $150 billion. Thus, covering gene therapy for a rare condition at a higher WTP represents an equitable conclusion to what payers currently expend for common chronic conditions.

The fourth point to note is that the opportunity cost of not addressing rare conditions with expensive, curative therapies is much greater than managing ongoing chronic conditions. A case of sickle cell disease left untreated results in continual years of pain, suffering, and over $50,000 in annual pain management fees, among other costs. A

high cost to eliminate the burden of the condition, plus suffering minimizes future costs and maximizes utility. Whereas a treatment for chronic disease management only prevents or delays the onset of future sequelae of conditions but does not increase the probability of the elimination of the index condition. This contrast further explains the reason for prevalence adjustment connected to relative risk. There is greater relative risk aversion in a patient who has a manageable condition rather than one who faces the ongoing immediate and existential threat of their condition, as patients with rare diseases often do.

The fifth point is that this adjustment for generalized CEA meets the demands of addressing the methodological need for dynamic prevalence. Dynamic prevalence itself simply implies that the prevalence of disease changes over time, and that CEA should somehow account for that fact. The design of *Eq. 21*, while representative of time fixed effects, permits one to map out shifts in WTP over time with shifts in prevalence, that is:

$$K(t) = \frac{M}{1-(Prevalence_t^2)^2} \tag{25}$$

Thus, as health technology introduces more efficient, potentially curative solutions, and prevalence approaches 0.0, WTP should increase since the technology represents an occasion to completely eliminate all opportunity costs of a condition in the future.

5.1 Limitations

This work has several limitations. First the assumption that the square an event in the exposed population is equal to the event in an exposed population by no event in the unexposed population could be interpreted as ***A=D***. This is maintained for conditions such as hypercholesterolemia or cancer, where the likelihood of the condition may occur as commonly based on hereditary (i.e. “exposed”) vs. environmental (i.e. “unexposed”)

conditions, or perhaps for diseases that could occur through a random genetic mutation. However, it may not be an appropriate assumption for infectious diseases (e.g. viral or bacterial infections), where the likelihood of disease shifts dramatically with exposure, thus making the assumption ***A=D*** *unlikely* (Bishai et al., 2023).

Second, we used hypercholesterolemia as a "singularity" for this analysis since it represents the most common condition in the U.S. population at the average WTP threshold of the Medicare program. The analysis is based on another assumption that in a condition that affects all of the population, that WTP is $0.0/QALY, since a condition that everybody has would be considered "normal," so why would society pay for it? There may in fact by other singularities where despite risk being universally accepted, the WTP is non-zero, such as for the polio vaccine. The appropriate singularities for this analysis to calibrate the curve for WTP over prevalence requires additional investigation of different conditions at known incremental cost-effectiveness ratios in equilibrium.

Third, the assumption that a disease reaches 0.0 prevalence with increased WTP remains entirely an assumption, since it is relatively unproven.

6. Conclusion

This paper examines the purpose for which WTP is empirically derived from disease prevalence through relative risk. Relative risk possesses overlapping definitions in economic and epidemiologic theory that facilitate the translation of prevalence into WTP for medical decision-making. The analysis suggests that WTP thresholds are correlated

with disease prevalence, and that there are exponential shifts in WTP as prevalence approaches zero cases.

All else being equal, nobody would choose to have a medical condition. Given that two different diseased populations of varying size would have the same WTP threshold may be unfair for the individuals in the smaller population, since manufacturers of health technology would be less likely to investigate solutions without greater reward. The Orphan Drug Act was designed to facilitate greater supply of medicines for rare diseases with <200,000 cases through tax credits, and extended periods of patent protection, market exclusivity, and higher branded prices as a result (Conti & Berndt, 2016). However, the 2017 Tax Cuts and Jobs Act reduced these tax credits, and as a result limited manufacturers' incentives to invest in rare disease markets. This model could curb that consequence but providing decision-makers with logical justification for why investment in rare disease indications at higher rates despite high prices could reduce opportunity costs to manage population health.

There are implications of this work for several key stakeholders. For individuals in health economics, this analysis represents a sliding scale by which one can apply a WTP threshold for a given generalized CEA. It also demands that one consider dynamic prevalence of disease over time as the needs of individuals are addressed through increased access to medicine, thereby reducing prevalence in a CEA model and further shifting WTP upward.

For individuals in decision-making, examining WTP against the costs and clinical benefits of medicine for a particular population is not a fixed process. Decision-makers can

used generalized dynamic prevalence to inform changes in WTP in a risk pool based on local rates of prevalence, independent of national trends. In doing so in the short-run, generalized CEA with dynamic prevalence based on an adjustable WTP threshold reduces opportunity costs to afford to treat other expensive conditions over the long-term.

Given the limited number of cases where CEA has strongly influenced medical resource allocation to date, and the resistance of decision-makers to use QALYs in the face of its bias against individuals with disabilities, this approach to generalized CEA using dynamic prevalence in terms of relative risk overcomes multiple obstacles. It likely addresses the limitations of the QALY since it is based on the established GRACE theoretical framework, thereby assuming non-constant shifts in health in the creation of utility. These shifts represent unequal risk for different individuals seeking care, and patients with increasing rarity are likely to also have increased risk. It also assists decision-makers in making feasible short- vs. long-term investments in the allocation of medical resources based on fair assumptions related to improvements in health utility for patients. Consistent with this, decision-makers can always use this approach to address unmet need among patients facing the greatest risk to depletion of health utility.

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References

Agency for Healthcare Research and Quality. (2023). *MEPS HC-231: 2021 Medical Conditions File*. Retrieved 09/18/2023 from https://meps.ahrq.gov/mepsweb/data_stats/download_data_files_detail.jsp?cboPufNumber=HC-231

Arthur, W. B. (1981). The Economics of Risks to Life. *The American Economic Review*, *71*(1), 54-64. http://www.jstor.org/stable/1805039

Attonito, J., Van Arsdale, W., Fishman, K., Darya, M., Jacomino, M., & Luck, G. (2021). Sociodemographic Disparities In Access To COVID-19 Vaccines Upon Initial Rollout In Florida. *Health Aff (Millwood)*, *40*(12), 1883-1891. https://doi.org/10.1377/hlthaff.2021.01055

Basu, A., Winn, A. N., Johnson, K. M., Jiao, B., Devine, B., Hankins, J. S., Arnold, S. D., Bender, M. A., & Ramsey, S. D. (2024). Gene Therapy Versus Common Care for Eligible Individuals With Sickle Cell Disease in the United States : A Cost-Effectiveness Analysis. *Ann Intern Med*, *177*(2), 155-164. https://doi.org/10.7326/m23-1520

Bertram, M. Y., Lauer, J. A., De Joncheere, K., Edejer, T., Hutubessy, R., Kieny, M. P., & Hill, S. R. (2016). Cost-effectiveness thresholds: pros and cons. *Bull World Health Organ*, *94*(12), 925-930. https://doi.org/10.2471/BLT.15.164418

Bhopal, R. S. (2016). The concept of risk and fundamental measures of disease frequency: Incidence and prevalence. In *Concepts of Epidemiology: Integrating the ideas, theories,*

principles, and methods of epidemiology (3rd Edition ed.). Oxford University Press. https://doi.org/10.1093/med/9780198739685.003.0007

Bishai, D., Brenzel, L., & Padula, W. V. (2023). *Handbook of Applied Health Economics in Vaccines*. Oxford University Press. https://doi.org/10.1093/oso/9780192896087.001.0001

Brekke, K. R., Dalen, D. M., & Straume, O. R. (2023). The price of cost-effectiveness thresholds under therapeutic competition in pharmaceutical markets. *J Health Econ*, *90*, 102778. https://doi.org/10.1016/j.jhealeco.2023.102778

Broome, J. (1991). *Weighing Goods: Equality, Uncertainty and Time*. Wiley-Blackwell.

Carroll, M. D., Fryar, C. D., & Nguyen, D. T. (2017). Total and High-density Lipoprotein Cholesterol in Adults: United States, 2015-2016. *NCHS Data Brief*(290), 1-8. https://www.ncbi.nlm.nih.gov/pubmed/29155686

Castanon, A., Sloan, R., Arocha, L. S., & Ramagopalan, S. V. (2024). EU HTA Joint Clinical Assessment: are patients with rare disease going to lose out? *J Comp Eff Res*, *13*(6), e240052. https://doi.org/10.57264/cer-2024-0052

Centers for Disease Control and Prevention. (2020, 2020-12-16T02:20:08Z). *Data & Statistics on Sickle Cell Disease | CDC*. Centers for Disease Control and Prevention,. Retrieved 04/20/2021 from https://www.cdc.gov/ncbddd/sicklecell/data.html

Centers for Medicare & Medicaid Services. (2022). *National Health Expenditure Data*. Retrieved 10/30/2024 from https://www.cms.gov/data-research/statistics-trends-and-reports/national-health-expenditure-data/nhe-fact-sheet#:~:text=The%20largest%20shares%20of%20total,the%20households%20(28%20percent).

Conti, R. M., & Berndt, E. R. (2016). *Specialty Drug Prices and Utilization after Loss of U.S. Patent Exclusivity, 2001–2007*.

Cubanski, J., Neuman T, True S, Damico A. (2019). How much does Medicare spend on insulin? *Kaiser Family Foundation*. Retrieved 16 July 2024, from https://www.kff.org/medicare/issue-brief/how-much-does-medicare-spend-on-insulin/

Dangerfield, C., Fenichel, E. P., Finnoff, D., Hanley, N., Hargreaves Heap, S., Shogren, J. F., & Toxvaerd, F. (2022). Challenges of integrating economics into epidemiological analysis of and policy responses to emerging infectious diseases. *Epidemics*, *39*, 100585. https://doi.org/10.1016/j.epidem.2022.100585

Garber, A. M., & Phelps, C. E. (1997). Economic foundations of cost-effectiveness analysis. *J Health Econ*, *16*(1), 1-31.

Garg, S. (2020). The "Economic Health" of U.S. Health Care and Role of Middlemen. *Diabetes Technol Ther*, *22*(2), 136-141. https://doi.org/10.1089/dia.2019.0395

Garrison, L. P., Pezalla, E., Towse, A., Yang, H., Faust, E., Wu, E. Q., Li, N., Sawyer, E. K., & Recht, M. (2021). Hemophilia Gene Therapy Value Assessment: Methodological Challenges and

Recommendations. *Value Health*, *24*(11), 1628-1633. https://doi.org/10.1016/j.jval.2021.05.008

Global Burden of Cardiovascular Diseases, C., Roth, G. A., Johnson, C. O., Abate, K. H., Abd-Allah, F., Ahmed, M., Alam, K., Alam, T., Alvis-Guzman, N., Ansari, H., Arnlov, J., Atey, T. M., Awasthi, A., Awoke, T., Barac, A., Barnighausen, T., Bedi, N., Bennett, D., Bensenor, I.,…Murray, C. J. L. (2018). The Burden of Cardiovascular Diseases Among US States, 1990-2016. *JAMA Cardiol*, *3*(5), 375-389. https://doi.org/10.1001/jamacardio.2018.0385

Gnardellis, C., Notara, V., Papadakaki, M., Gialamas, V., & Chliaoutakis, J. (2022). Overestimation of Relative Risk and Prevalence Ratio: Misuse of Logistic Modeling. *Diagnostics (Basel)*, *12*(11). https://doi.org/10.3390/diagnostics12112851

Goshua, G., Calhoun, C., Ito, S., James, L. P., Luviano, A., Krishnamurti, L., & Pandya, A. (2023). Distributional Cost-Effectiveness of Equity-Enhancing Gene Therapy in Sickle Cell Disease in the United States. *Ann Intern Med*, *176*(6), 779-787. https://doi.org/10.7326/M22-3272

Griffin, S., Walker, S., & Sculpher, M. (2020). Distributional cost effectiveness analysis of West Yorkshire low emission zone policies. *Health Econ*, *29*(5), 567-579. https://doi.org/10.1002/hec.4003

Karmarkar, T., Rodriguez-Watson, C. V., Watson, E., Zheng, H., Gaskin, D. J., & Padula, W. V. (2022). Value of Triage Treatment Strategies to Distribute Hepatitis C Direct-Acting

Antiviral Agents in an Integrated Healthcare System: A Cost-Effectiveness Analysis. *Value Health*, *25*(9), 1499-1509. https://doi.org/10.1016/j.jval.2022.03.003

Lakdawalla, D. N., Doshi, J. A., Garrison, L. P., Jr., Phelps, C. E., Basu, A., & Danzon, P. M. (2018). Defining Elements of Value in Health Care-A Health Economics Approach: An ISPOR Special Task Force Report [3]. *Value Health*, *21*(2), 131-139. https://doi.org/10.1016/j.jval.2017.12.007

Lakdawalla, D. N., & Phelps, C. E. (2021). Health technology assessment with diminishing returns to health: the Generalized Risk-Adjusted Cost-Effectiveness (GRACE) approach. *Value Health*, *24*(2), 244-249.

Matthies, K., & Toxvaerd, F. (2022). Rather doomed than uncertain: risk attitudes and transmissive behavior under asymptomatic infection. *Econ Theory*, 1-44. https://doi.org/10.1007/s00199-022-01448-y

McDougall, J. A., Furnback, W. E., Wang, B. C. M., & Mahlich, J. (2020). Understanding the global measurement of willingness to pay in health. *J Mark Access Health Policy*, *8*(1), 1717030. https://doi.org/10.1080/20016689.2020.1717030

Meltzer, D. (2001). Addressing uncertainty in medical cost-effectiveness analysis implications of expected utility maximization for methods to perform sensitivity analysis and the use of cost-effectiveness analysis to set priorities for medical research. *J Health Econ*, *20*(1), 109-129. https://doi.org/10.1016/s0167-6296(00)00071-0

Mulligan, K., Baid, D., Doctor, J. N., Phelps, C. E., & Lakdawalla, D. N. (2024). Risk preferences over health: Empirical estimates and implications for medical decision-making. *J Health Econ*, *94*, 102857. https://doi.org/10.1016/j.jhealeco.2024.102857

National Center for Advancing Translational Sciences. *Genetic and Rare Diseases Information Center: Duchenne muscular dystrohpy*. Retrieved 10/14/2024 from https://rarediseases.info.nih.gov/diseases/6291/duchenne-muscular-dystrophy

National Institute of Standards and Technology. *Box-Cox Normality Plot*. Retrieved 09/01/2023 from https://www.itl.nist.gov/div898/handbook/eda/section3/eda336.htm

Noussair, C. N., Trautmann, S. T., & Van de Kuilen, G. (2014). Higher order risk attitudes, demographics, and financial decisions. *Rev Econ Studies*, *81*(1), 325-355.

Oussedik, E., Anderson, M. S., & Feldman, S. R. (2017). Risk versus benefit or risk versus risk: Risk aversion in the medical decision making process. *J Dermatolog Treat*, *28*(1), 1-2. https://doi.org/10.1080/09546634.2017.1290575

Padula, W. V., & Kolchinsky, P. (2024). Can Generalized Cost-effectiveness Analysis Leverage Meaningful Use of Novel Value Elements in Pharmacoeconomics to Inform Medicare Drug Price Negotiation? *Value Health*. https://doi.org/10.1016/j.jval.2024.04.013

Padula, W. V., Levin, J. S., Lee, J., & Anderson, G. F. (2021). Cost-effectiveness of total state coverage for hepatitis C medications. *Am J Manag Care*, *27*(5), e171-e177. https://doi.org/10.37765/ajmc.2021.88640

Phelps, C. E., & Cinatl, C. (2021). Estimating optimal willingness to pay thresholds for cost-effectiveness analysis: A generalized method. *J Health Econ*, *30*(7), 1697-1702.

Philipson, T. (1999). Economic Epidemiology and Infectious Diseases. *National Bureau of Economic Research Working Paper Series*, *No. 7037*. https://doi.org/10.3386/w7037

Pronovost, P. J., Urwin, J. W., Beck, E., Coran, J. J., Sundaramoorthy, A., Schario, M. E., Muisyo, J. M., Sague, J., Shea, S., Runnels, P., Zeiger, T., Topalsky, G., Wilhelm, A., Palakodeti, S., & Navathe, A. S. (2021). Making a Dent in the Trillion-Dollar Problem: Toward Zero Defects. *2*(1). https://doi.org/doi:10.1056/CAT.19.1064

Ramagopalan, S. V., Diaz, J., Mitchell, G., Garrison, L. P., Jr., & Kolchinsky, P. (2024). Is the price right? Paying for value today to get more value tomorrow. *BMC Med*, *22*(1), 45. https://doi.org/10.1186/s12916-024-03262-w

Rothman, K. J., Greenland S, Lash TL. (2008). *Modern Epidemiology*. Lippincott, Williams and Wilkins.

Speller, J., Rayel S. (2023). New Analysis of Sickle Cell Disease Prevalence Among Medicaid Enrollees Fills Gap in Public Data. *Spotlight on Health*. Retrieved 16 July 2024, from https://www.norc.org/research/library/spotlight-new-analysis-of-sickle-cell-disease-prevalence-among-medicaid-enrollees.html

Sumarsono, A., Lalani, H. S., Vaduganathan, M., Navar, A. M., Fonarow, G. C., Das, S. R., & Pandey, A. (2021). Trends in Utilization and Cost of Low-Density Lipoprotein Cholesterol-

Lowering Therapies Among Medicare Beneficiaries: An Analysis From the Medicare Part D Database. *JAMA Cardiol*, *6*(1), 92-96. https://doi.org/10.1001/jamacardio.2020.3723

Troy, A., & Anderson, T. S. (2021). National Trends in Use of and Spending on Oral Anticoagulants Among US Medicare Beneficiaries From 2011 to 2019. *JAMA Health Forum*, *2*(7), e211693. https://doi.org/10.1001/jamahealthforum.2021.1693

Vanness, D. J., Lomas, J., & Ahn, H. (2021). A Health Opportunity Cost Threshold for Cost-Effectiveness Analysis in the United States. *Ann Intern Med*, *174*(1), 25-32. https://doi.org/10.7326/M20-1392

Verweij, M., & Dawson, A. (2019). Sharing Responsibility: Responsibility for Health Is Not a Zero-Sum Game. *Public Health Ethics*, *12*(2), 99-102. https://doi.org/10.1093/phe/phz012

von Neumann, J., Morgenstern, O., & Rubinstein, A. (1944). *Theory of Games and Economic Behavior (60th Anniversary Commemorative Edition)*. Princeton University Press. http://www.jstor.org/stable/j.ctt1r2gkx

Woods, B., Revill, P., Sculpher, M., & Claxton, K. (2016). Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. *Value Health*, *19*(8), 929-935. https://doi.org/10.1016/j.jval.2016.02.017

Woolson, R. F., & Bean, J. A. (1982). Mantel-Haenszel statistics and direct standardization. *Stat Med*, *1*(1), 37-39. https://doi.org/10.1002/sim.4780010106

Zhang, J., & Yu, K. F. (1998). What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *Jama*, *280*(19), 1690-1691. https://doi.org/10.1001/jama.280.19.1690