

VALUE & OUTCOMES SPOTLIGHT

A magazine for the global HEOR community.

PATIENTS VS PROCESS

The Data and the Drivers Behind Patient-Centered Outcomes

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Putting the Patient Voice First: Novel Approaches to Incorporating Patient-Centered Outcomes in Value Assessment

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For more than 55 years, the PhRMA Foundation has been helping advance scientific research and innovation to benefit patients. Our mission is to improve public health by proactively investing in innovative research, education, and value-driven healthcare. Illustrative of this objective is our Value Assessment Initiative that promotes the development of advanced value assessment frameworks and methodologies that are rigorous, transparent, and address the needs of all healthcare stakeholders, including patients, payers, and providers. Recently, we have sharpened our focus on patient centricity and health equity as key pillars of the value assessment framework development process.

In 2017, we began funding the **Challenge Awards** as a way to foster new, innovative research concepts that can build on a growing field of study aimed at advancing patient-centeredness in value assessment. Each year, a pressing question related to value assessment in healthcare is distributed and researchers are invited to submit proposals in response.

High-quality and efficient healthcare should seek to improve outcomes that matter most to patients and society. Efforts to measure value in healthcare should recognize that the value of an intervention may vary depending on the outcomes it produces in treating a specific disease or according to the characteristics and preferences of the patient. However, increasing focus on patient-centered health services research has revealed gaps between the outcomes that patients report are most important to them and the outcomes traditionally measured in value assessment.

We have sharpened our focus on patient centricity and health equity as key pillars of the value assessment framework development process.

As such, there is increased recognition that if value assessment is to play a more meaningful role in healthcare decision making in the United States, better definitions and methods for assessing value must be developed to appropriately account for patient perspectives.

Patient-centered outcomes can be defined as the outcomes important to patients in the way they experience a disease or a treatment for that disease. Patient-centered outcomes may include a range of measures: clinical (mortality, biomarkers), patient-reported outcomes (symptoms, function, preferences),

treatment-related attributes (mode of administration), resource availability and use (hospitalizations), and/or societal impacts (productivity, caregiver burden).

In addition, small differences in individual characteristics—such as age or health status, race and ethnicity, and personal experience—as the result of systemic barriers (eg, bias and discrimination), biological differences, and personal preferences can significantly alter a medicine's clinical effect or patients' perceptions of value.

Until significant progress is made to capture, measure, and operationalize patient-centered outcomes, defining the true value of a healthcare intervention will remain a challenging endeavor.

Important patient-centered outcomes and patient differences are often omitted from traditional approaches to value assessment methods and processes, which tend to focus on a selected subset of clinical outcomes simply because these are the endpoints studied in trials.

In this special supplement to *Value & Outcomes Spotlight*, we are very pleased to share our **2020 Challenge Award**-winning papers that inform the development and inclusion of patient-centered outcomes into value assessment.

The 4 winning teams were selected from among dozens of submissions that sought solutions to the following question:

What approaches are needed to consistently and reliably incorporate patient-centered outcomes in value assessment for both population- and individual-level healthcare decision making?

The **2020 Challenge Award** papers in this series include a novel approach to measuring disease severity in economic models¹; a set of practical guidelines for identifying and including patient-centered outcomes in value assessment²; a framework to empower care teams to ensure treatment decisions are tailored toward patient needs³; and a demonstration for how the coproduction method can improve the healthcare system for people with a specific disease state—in this case, epilepsy.⁴

These efforts—and the work of many others—are having a meaningful impact on ensuring that value assessment reflects

what matters most to patients. Until significant progress is made to capture, measure, and operationalize patient-centered outcomes, defining the true value of a healthcare intervention will remain a challenging endeavor.

The PhRMA Foundation is pleased to share the work of these leading researchers in the field of value assessment and encourages *Value & Outcomes Spotlight* readers to share these award-winning concepts with your colleagues. •

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Generalized Risk-Adjusted Cost-Effectiveness (GRACE): Ensuring Patient-Centered Outcomes in Healthcare Decision Making

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SUMMARY

Cost-effectiveness analysis (CEA) is widely used to assess health technology but embeds an assumption at odds with most economic analysis and that conflicts with established understanding of people's preference patterns. It assumes that health produces happiness with no diminishing returns, in conflict with both standard economic thinking and normal human intuition. Our Generalized Risk-Adjusted Cost-Effectiveness (GRACE) analysis allows diminishing returns to health and aligns CEA with the rest of the health economics literature. This simple change has far-reaching implications for the practice of CEA. In GRACE, optimal cost-effectiveness thresholds are systematically higher for more severe diseases and lower for milder ones than when using standard CEA. We provide formulae for estimating how these thresholds vary with health-related quality of life (QoL) in the sick state. Finally, we provide a coherent way to combine improvements in QoL and life expectancy when people have diminishing returns to QoL. This new approach obviates the need for increasingly prevalent and ad hoc exceptions to CEA for end-of-life care, rare disease, and very severe disease (eg, cancer). Our methods also show that the value of improving QoL for people with disabilities is greater than for comparable people without disabilities, while also incorporating a key patient-preference perspective that QoL gains are more highly valued than life-year extensions for the sickest or most-disabled people. The GRACE model ensures—more than any known system to measure value in healthcare—that patients' preferences, particularly the quintessential measure of untreated health status, reliably and consistently enter value measures used at both population and individual decision making. This analysis complements and adds to our previous analyses demonstrating how best to incorporate uncertain health benefits into value analyses.

Introduction

Suppose you had psoriasis or acid reflux. Standard cost-effectiveness analysis (CEA) methods would measure your quality of life (QoL) at around 0.9 on a health-index scale from 0 (worst health you can imagine) to 1 (ideal health). How much would you pay for a perfect cure, adding 0.1 extra QoL units? Would it be more than, less than, or the same as what you would pay for 0.1 extra QoL units if you were instead in the latter stages of Duchenne muscular dystrophy (DMD), the ravages of which have left you with 0.25 QoL?

Standard CEA says that improving QoL by 0.1 in each of these very different situations is equivalent. Both intuition and survey data reject this conclusion. Survey respondents regularly state that the same QoL improvement is worth more when given to people in worse health states.¹⁻⁴ Why does CEA fail to capture this feature of patient preferences, and what does this mean for its other predictions? In particular, the key assumption in standard CEA that leads to the failure to capture the effect of untreated health status also leads directly to 2 other puzzling conclusions. The first is that uncertainty in treatment outcomes does not matter. The second is that people's willingness to trade life expectancy for QoL improvements (or vice versa) does not vary with baseline QoL.

Standard CEA models decompose health gains into 2 parts: (1) gains in QoL, weighted by remaining (baseline) life expectancy, and (2) gains in life expectancy, weighted by baseline QoL. In this model, a given gain in life expectancy is always worth less to sicker or more-disabled people because life expectancy gains are weighted by lower QoL. Similarly, QoL gains are downgraded if the disability reduces life expectancy. This implication has triggered objections that CEA discriminates

Cost-effectiveness analysis has fallen out of step with the rest of health economic research. GRACE aligns the economics of CEA with the human circumstances of patients. It rewards interventions that promote equity and provide relief to patients most in need.

against people with disabilities.^{4,5} Concern about this issue, among others, led to prohibition of using CEA in the United States to measure value in studies by the Patient-Centered Outcomes Research Institute or to determine coverage of medical treatments in Medicare.¹

¹Specifically, Section 1182, 42 U.S.C. 1320e-1(c(1)) reads: "The Patient-Centered Outcomes Research Institute established under section 1181(b)(1) shall not develop or employ a dollars-per-quality adjusted life-year (or similar measure that discounts the value of a life because of an individual's disability) as a threshold to establish what type of healthcare is cost-effective or recommended. The Secretary shall not utilize such an adjusted life-year (or such a similar measure) as a threshold to determine coverage, reimbursement, or incentive programs under title XVIII."

Proponents of CEA say that it has never been used to discriminate against those who are disabled, so there is no problem. However, even absent explicit discrimination, CEA value measurements can influence how healthcare resources are allocated to people with highly severe illnesses and disabilities, how healthcare innovations are reimbursed, and hence, how research and development for new therapies is incentivized.

Several models have been proposed to “fix” this anomaly in CEA. First, the Equal Value of Lives (EVL) method imputes full QoL to disabled people when estimating the value of treatments to resolve their conditions.⁶ Subsequent research proposed the Healthy Years in Total (HYT) model, which also assumes perfect QoL when valuing gains in life expectancy but adds extra value for gains in QoL itself.⁵ Both methods address the disability bias issue by assuming ideal QoL when assessing gains in life expectancy. Several European HTA organizations have also considered “proportional shortfall” in health caused by a particular disease as the basis for equity-based weighting of treatment value, but with an ad hoc basis proposed to derive such weights.⁷

What’s missing from standard cost-effectiveness analysis? Quite simply, it omits consideration of patients’ starting point—“how sick am I?”

Within these approaches, analysts must either abandon the rigorous theoretical framework of traditional CEA or employ it while assuming QoL levels that depart from reality. We agree with this issue’s importance, but we believe that these approaches paint over still-unrepaired cracks in the theoretical foundation of CEA.

Instead, we focus on the foundational problem with traditional CEA—its failure to properly reflect how rational consumers would value health improvements in different contexts. Addressing this problem, we analyze how consumers answer fundamental questions about value: (1) “What is my untreated QoL?” and based on that answer, (2) “How much would I value improvements in QoL and additions to life expectancy?” Our model uses a composite measure of health, summarizing multiple dimensions of value into a single composite score (eg, as in EQ-5 health index or comparable multicriteria decision analysis methods).

We use neoclassical economic analysis tools upon which traditional CEA was built, but we eliminate the troublesome and unrealistic assumptions leading to rickety foundations for value assessment. Our analysis reveals how traditional methods fail to account for disease severity, patient risk aversion, and other issues. We prove mathematically that cost-effectiveness thresholds should be higher for more-severe illnesses, and

that QoL gains are more valuable to those with worse QoL, whether arising from illness, disability, or combinations thereof. These implications will influence how healthcare resources and innovation investments should be allocated and how medical technology ought to be reimbursed. This analysis extends in new directions our recent study on how uncertainty enters proper value measurement of risk-averse consumers.⁸

Beyond CEA: Amazing GRACE

Grace: A “polite and thoughtful way of behaving.”

What’s missing from standard CEA? Quite simply, it omits consideration of patients’ starting point—“how sick am I?” People with low QoL will value gains in QoL more than people with greater QoL. Economists call this “diminishing returns.” If you have \$100,000 in annual income, \$5000 more does not mean as much as when you have \$15,000 annual income. If you live in a 5000 square-foot home, adding another 500 square feet is less valuable than if you live in a 1000 square-foot home. In all phases of life, economists observe diminishing returns, formally called “diminishing marginal utility.”

Standard CEA models incorporate diminishing returns in consumption of nonhealth goods and services—things we buy every day. But when it comes to QoL itself, the standard CEA model quite differently assumes that there are no diminishing returns to QoL as it contributes to happiness (utility). This stance is unusual. Indeed, the assumption of diminishing returns to health-related QoL is axiomatic in virtually all of health economics,⁹⁻¹⁵ *except for CEA*. We very briefly explore how this assumption distorts the mathematics of cost-effectiveness and then turn to its implications for patient-centered value assessment.

Traditional CEA calculates the incremental cost-effectiveness ratio—added cost (compared to the next-best alternative) divided by added health benefits—and then compares this ratio to a maximum “willingness to pay” cutoff for healthcare, which we will call K .^{16,17} This willingness-to-pay value is the ratio of income available for consumption, C , to a measure of how quickly diminishing returns set in when consuming nonhealth goods and services. Intuitively, the faster diminishing returns set in on nonhealth consumption, the less “pain” there is in shifting resources to buy medical care. This summary measure of the speed of diminishing returns, ω_C , measures the percent gain in utility generated by one percent additional income. If $\omega_C = 1$, then there are no diminishing returns, but with diminishing returns, then $\omega_C < 1$. Current evidence suggests that $0.3 < \omega_C < 0.5$.¹⁶

In the traditional CEA framework, willingness to pay is $K = C / \omega_C$. Existing estimates for ω_C then imply the willingness-to-pay threshold for CEA is about 2 to 3 times the annual consumption-related income, C . Disease severity and disability do not matter. Once we relax the standard model’s restrictive assumption of nondiminishing returns in QoL, however, wholly different results emerge.

We call our revision to the theory the GRACE model. It changes the willingness-to-pay measure in 2 key ways. First, a new term emerges that accounts for how rapidly returns to health, H , diminish. In parallel to the measure for consumption, we define this speed of diminution as ω_H . It has the same meaning as ω_C , except that it relates to health-related QoL instead of nonhealth consumption. Second, willingness to pay in GRACE also depends on an index of illness severity (R), which climbs exponentially as baseline QoL degrades. **Table 1** provides examples of this pattern for some representative diseases.

Quantitatively, R is the ratio of the marginal utility of health in the sick state to the marginal utility when healthy. Combining these 2 changes, the GRACE measure of willingness to pay is not $K = C / \omega_C$, but instead is $K_{GRACE} = CR [\omega_H / \omega_C] = K \omega_H R$. Compared to traditional CEA, GRACE implies lower willingness to pay for treating mild illness (since $0 < \omega_H < 1$ and $R \approx 1$ for mild illnesses) but significantly higher willingness to pay for severe illness (since R grows exponentially with illness severity). Traditional CEA causes us to overpay for treatments of mild illnesses but underpay for treatments of severe illnesses.⁸

By how much are we underpaying for severe illness? The answer to that question depends on how rapidly the incremental value of health changes as the baseline level of health changes. Economists have long understood that the presence and speed of diminishing returns are both linked to a concept called “risk aversion.” Diminishing returns means that 1 unit of consumption—or of health—is worth less to someone who starts with more of it. In turn, this implies that consumers fear the downside of losing 1 unit of consumption more than they value the upside of gaining 1 more unit. Therefore, consumers exhibiting diminishing returns would rather avoid taking risks—even ones whose downside is exactly equal to its upside, like those weighted by the toss of a fair coin. This avoidance of “fair” risky outcomes is the textbook definition of “risk aversion.” In parallel, diminishing returns to QoL imply that patients are averse to taking risks with their health-related QoL. In other words, by ruling out diminishing returns to health-related QoL,

traditional CEA assumes—we believe incorrectly—that patients are unconcerned about risks associated with their health and treatment outcomes.

GRACE provides a path forward that accounts for the cost of health-related risks and explains the intuition that disease severity affects value assessment. The standard economist’s measure of “relative risk aversion” over nonhealth consumption is r_C^* .ⁱⁱ The GRACE model allows for a parallel concept, relative risk aversion in health, denoted as r_H^* . Standard CEA implicitly assumes that $r_H^* = 0$ (ie, patients find it costless to bear risks in their QoL). When we allow instead for values of $r_H^* > 0$, the proper way to value gains in health changes dramatically. Now untreated health status—the quintessential patient-centered determinant of value in health—influences willingness to pay for health gains.

To assess the importance of this issue, we need 1 further definition. Again, using QoL scales from 0 (worst health state that you can imagine) to 1 (ideal health), think of a health loss ℓ^* measuring the relative change from ideal health. Along this scale, $\ell^* = 0.1$ is a relatively small loss in QoL, going from ideal health to QoL = 0.9. Alternatively, if $\ell^* = 0.5$, your health loss would be 50% of the way from “ideal” to “worst imaginable,” and QoL = 0.5. If $\ell^* = 0.9$, the resulting QoL is 0.1. You would be very, very sick.

Table 1 gives QoL levels for some exemplary diseases or disabling conditions, all drawn from the Tufts University Cost-Effectiveness Analysis Registry (CEAR) data.¹⁸ As this table shows, diseases and health conditions that create very large health losses ($\ell^* > 0.8$) contain many disorders that people think of as very bad health outcomes.

The last piece of the puzzle is the magnitude of r_H^* . We do not yet have direct measures of this key parameter, but we have good evidence on comparable measures of risk aversion in consumption placing r_C^* at about 1.0, perhaps a bit lower or higher.¹⁹ With no other evidence yet available, we assessed the effects of severity of illness on willingness to pay over a range of

Table 1: Example diseases for various levels of ℓ^* .

ℓ^*	Example Diseases
0.0-0.1	Peptic Ulcer Disease; Stress Urinary Incontinence; Benign Prostatic Hyperplasia
0.1-0.2	Grave’s Disease; Hypertension with no complications; Sleep Apnea
0.2-0.3	Familial Hypercholesterolemia; Peripheral Arterial Disease; End-Stage Knee Osteoarthritis
0.3-0.5	Type 1 Diabetes; Acute Lung Injury; Moderate to Severe Rheumatoid Arthritis
0.5-0.7	TIA ^a and Carotid Stenosis; TBI ^b ; Nursing Home Residents at Risk of Pressure Ulcers
0.7-1.0	Alzheimer’s disease; Metastatic Colorectal Cancer; Acute Pulmonary Embolism

^a Transient ischemic attack

^b Traumatic brain injury

Source: Lakdawalla and Phelps [8]

ⁱⁱ Formally, where $U(C)$ is the utility of a given level of consumption, relative risk aversion in consumption is given by $r_C^* = -CU''(C) / (U'(C))^2$. It measures how fast marginal utility changes as the level of consumption changes.

values for r_H^* . If there were a column in Table 2 corresponding to a value of $r_H^* = 0$, every entry would be 1.0.

We now turn back to R, the disease severity ratio. As R rises, so does the willingness-to-pay threshold implied by GRACE. The R multiplier depends on relative risk aversion in QoL, r_H^* , and the QoL loss from the disease, ℓ^* . Therefore, accurate implementation of the GRACE model will require good estimates of both these parameters. Fortunately, risk aversion over QoL can be estimated “only once” and need not be repeatedly estimated in each specific disease or therapeutic context. It can be estimated with common and well-understood discrete choice experimental methods.²⁰ Moreover, ℓ^* is already routinely estimated by “burden of illness” studies and requires no new or specialized estimates. **Table 2** illustrates how R varies with both these parameters.

To see how **Table 2** works, assume that $r_H^* = 1$, similar to central estimates for r_C^* . Now read down the column under $r_H^* = 1$ in **Table 2**. For low-severity diseases with little QoL loss, R barely exceeds 1.0. As disease severity increases to $\ell^* = 0.5$ (see **Table 1** for exemplary diseases), $R = 2$, doubling the value per QoL improvement compared to very mild illnesses. As ℓ^* reaches 0.7, R grows to 3.33, and for $\ell^* = 0.9$ —very serious conditions— $R = 10$. Over a reasonably comprehensive range of $0.7 < r_H^* < 1.3$, R varies from 5 to almost 20 for high-severity illnesses. Therefore, the value of improving QoL these conditions (at the margin) is 5 to 20 times larger than for creating similar improvements for low-severity conditions. The same result holds for people with permanent disability—improving their QoL adds great value for severely disabling conditions, in stark contrast to standard CEA measures that lower the value of such improvements.

GRACE predicts that people would give up more than 3 times the life expectancy in exchange for this quality of life gain, because they place greater value on gains in quality of life.

If the degree of risk aversion in QoL is close to that of risk aversion in consumption, we estimate that the cost-effectiveness threshold for treating mild illness should be around \$50,000.⁸

Table 2 then implies that corresponding thresholds for highly severe illnesses will range from \$250,000 up to \$1,000,000 per quality-adjusted life-year (QALY) gained. This contrasts with traditional CEA approaches that assume cost-effectiveness thresholds are largely fixed, sometimes with ad hoc exceptions for rare or severe diseases.²¹

As noted earlier, some European studies propose using proportional shortfall in QALYs caused by a disease as the basis for equity weights to increase imputed value for those in

Table 2: R multiplier values in GRACE model for $0 < r_H^* \leq 1.3$.

	r_H^*								
ℓ^*	0.25	0.5	0.7	0.8	0.9	1	1.1	1.2	1.3
0	1	1	1	1	1	1	1	1	1
0.1	1.03	1.05	1.08	1.09	1.1	1.11	1.12	1.13	1.15
0.3	1.09	1.2	1.28	1.33	1.39	1.43	1.48	1.53	1.59
0.5	1.19	1.41	1.62	1.74	1.87	2	2.14	2.3	2.46
0.7	1.35	1.83	2.32	2.62	3.01	3.33	3.76	4.24	4.78
0.9	1.78	3.15	5.01	6.29	7.91	10	12.51	15.73	19.79

worse health. Our GRACE method provides an economically grounded way of creating the value weights for different disease severity, as distinct from the ad hoc methods suggested in some applications of “proportional shortfall” valuation.

Extensions in Life Expectancy

Acknowledging diminishing returns to and risk aversion over QoL reveals when and how disease severity affects the value of medical technology. GRACE, like virtually all of the standard health economics literature, assumes that people do not have diminishing returns in *life expectancy* (as opposed to QoL). It also shares this assumption with traditional CEA. Even so, differences in survival valuation still emerge between GRACE and traditional CEA. In the traditional model, the value of extending the probability of survival, p, (ie, life expectancy) is $\Delta p \times \text{Baseline QoL}$. GRACE adds one more term: the value of extending life expectancy must also account for the greater relative willingness to pay for QoL improvements as QoL falls. When people have very low QoL, they are willing to trade more life expectancy to gain improvement in QoL. This is, again, a simple consequence of diminishing returns to QoL.

An example demonstrates this concept using familiar time tradeoff methods. Suppose some people with degenerative knee disease had QoL scores of 0.75, so improvements to full health would add 0.25 to QoL. Suppose these people would give up 0.5 life-years out of 10 remaining expected life-years. Then the tradeoff rate would be $0.25/0.5 = 5$ additional QoL units demanded per each expected life-year lost.

In contrast, imagine some otherwise-similar people suffering a severe illness such as Alzheimer’s disease or Parkinson’s disease, with a QoL of 0.25. Among this group of people, an improvement to full health would gain 0.75 in QoL score, 3 times the QoL gain as for the “bum knee” patients. However, GRACE predicts that people in this group would give up *more than 3* times the life expectancy in exchange for this QoL gain, because they place greater value on gains in QoL. People with greater disability or sickness level are more willing to give up life-years for QoL improvement. This also inherently means they are less willing to give up QoL for life extension.

For given levels of income, people in worse QoL states will have lower willingness to pay for life-years and greater willingness to pay for QoL. Patients’ health context matters when it comes

to valuing medical technology. Traditional CEA implies that “a QALY is a QALY is a QALY....” This implication rests on the flawed assumption that the returns to QoL do not diminish. Further, it produces the problematic result that QALY gains are less valuable to sicker or more-disabled people. According to GRACE, the value of health gains to the disabled might be higher or lower: QoL gains are worth more, but the value of pure life expectancy gains remains ambiguous.ⁱⁱⁱ This incorporates patients’ circumstances in ways that traditional CEA methods overlook.

Applications in Decision Making

We see 4 levels of decision making where application of GRACE could move healthcare decisions towards more patient-centered outcomes.

The first step in the decision-making ladder involves health plans’ coverage determinations (those of individual plans or national plans such as the BNHS/NICE in the United Kingdom). For QoL gains, GRACE would reduce values for mild-disease treatments, but greatly increase them for interventions treating high-severity diseases. Full adaptation of GRACE would shift portfolios of covered services towards more-severe diseases, possibly leaving low-severity diseases outside of covered services, as Denmark’s national health plan does now.²² The GRACE model clearly emphasizes that treatments of sicker people have more value, so wider adoption of GRACE would lead to more use of severity-of-illness-based decision thresholds.

Next in the decision ladder comes prior authorization and other formulary restriction rules. Insurance companies do not have different rules for disabled and nondisabled when it comes to applying rules of access to approved treatments, but they regularly exclude coverage of “experimental” treatments, which will most often affect those with the lowest health status. GRACE leads to greater, not reduced access to such interventions for severely sick or disabled persons.

Third, properly constructed decision-support models using the GRACE model could also assist in individual decision making,

giving proper “advice” based on patients’ severity of illness (eg, in choosing among alternative cancer therapies).

Finally, as adoption of the GRACE method expands, responding to the shift in reimbursement, research, and development efforts of biotechnology companies and medical centers should shift towards discovery of interventions (drugs, devices, or new procedures) that provide benefit to the most severely ill. As these shifts in research and development occur, new technologies will provide more QoL gains than would occur using current CEA methods, the primary beneficiaries being those with the worst QoL status (pre-existing disease or disability). This approach would also promote equity along the specific dimension of severity of illness because those in the worst health will receive the greatest efforts towards improvement. To the extent that severity of illness is correlated with other measures of inequity, such as socioeconomic class or race, shifting to more generous payments for treatment of severe diseases would also indirectly benefit people along other dimensions of equity.

CEA has fallen out of step with the rest of health economic research. In the process, it has also excised recognition of how patients’ circumstances affect the value of treatment. Health improvements come in an array of types. Consequently, the “QALY is a QALY is a QALY” mantra comes off as especially jarring to real-world patients. It has also long troubled leading practitioners of and advocates for the use of CEA.^{24,25} In contrast, GRACE aligns the economics of CEA with the human circumstances of patients. It rewards interventions that promote equity and provide relief to patients most in need.

No other measure of patient-centered value measurement exists, we believe, that incorporates the most fundamental questions on the minds of people who are ill or have disabilities: “How sick am I?” and “How much value would I place on improving my QoL?” That, we believe, is the ultimate test of whether a value measurement system is truly patient centered. ●

ⁱⁱⁱ Recent analysis by the authors²³ shows how the value of LE gains could either rise or fall as disability increases.

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Nudging Health Economists: A Process for Systematic Identification of Patient-Centered Outcomes for Inclusion in Value Assessment

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SUMMARY

Consistently and reliably incorporating patient-centered outcomes within value assessment cannot be onerous or overly burdensome for patients or economic researchers. Approaches to identify, synthesize, and disseminate patient-centered outcome data in a way that can facilitate the inclusion of these outcomes in more cost-effectiveness analyses and value assessments must ideally be practical and feasible, or they will be met with resistance, which could mitigate the impact a patient-centered approach can have on rigor, validity, and use of findings. Thus, the objective of this paper is to provide practical guidance on a process of identifying and presenting patient-centered outcomes in a way that makes it easier to include in value assessment, thereby nudging more economists to choose to include these in their models. The process includes forming a multistakeholder, patient-centered advisory board, engaging the board in the research agenda, conducting evidence synthesis and qualitative research to ensure viewpoints are not missed, and disseminating findings to multistakeholder audiences. Finally, a publicly available, centralized database of identified patient-centered value elements should be created to increase the likelihood of their uptake in value assessment.

Introduction

Value assessment is intended as a tool for evaluating healthcare treatments to gauge value and inform decisions.¹ Many existing value assessments fail to account for all “elements of value” that may be important to payers, society, and—most importantly—patients (eg, treatment tolerability, productivity, time, fear of contagion, spillovers, hope, social impact).^{2,3} Value assessments typically incorporate cost-effectiveness analysis (CEA), focusing on costs and outcomes important to payers, missing important information to optimize resource allocation at a societal level.^{4,5} The societal perspective is likely the closest we have to a patient-centered model, but that is only true if the outcomes selected are also what patients care about.^{6,7} A recent review of 6907 CEAs found that many studies reporting a societal perspective were actually mislabeled.⁵ Further, when CEAs do incorporate variables for a “societal perspective” model, they frequently lack high-quality evidence to support the assumptions for these unique elements of value. These analytical difficulties have even led experts to recommend that the field embrace these challenges and adopt a standard for a “limited societal perspective” that attempts to incorporate time costs, opportunity costs, and community preferences.⁸

As value assessments are developed, the sources of evidence, methods, and assumptions of the underlying model may vary greatly between organizations or between assessments by the same organization.⁹ The Second Panel on Cost-Effectiveness in Health and Medicine further identified the process of evidence synthesis for CEAs as a key area for further work needed in the field, citing a lack of underlying theory guiding which studies to synthesize, assessing how studies may be biased, and assessing how findings generalize to a target population.¹⁰ A recent systematic review of cost-of-illness evidence for hepatitis C virus

infection described significant challenges in quantifying the full disease burden due to significant heterogeneity in identification of different types of costs, high risk of bias for many common cost variables, and difficulty in capturing some components reported by patients (eg, fear of harming others, insurance issues, or stigma).¹¹ Attempting to determine the value for a new treatment without considering all of the evidence or without adjusting for bias in included evidence may produce biased results or findings that are difficult to validate.

These failings cannot be fully dismissed by simply describing them in a “limitations” section without raising the question: *Would value assessment be better if we more intentionally capture commonly neglected elements of value?* However, this question poses a challenge. Consistently and reliably incorporating patient-centered outcomes within value assessment cannot be onerous or overly burdensome for patients or economic researchers. Approaches to identify, synthesize, and disseminate patient-centered outcome data in a way that can facilitate the inclusion of these outcomes in more CEAs and value assessments must ideally be practical and feasible, or they will be met with resistance, which could mitigate the impact a patient-centered approach can have on rigor, validity, and use of findings. Thus, the objective of this paper is to provide practical guidance on a process of identifying and presenting patient-centered outcomes in a way that makes it easier to include in value assessment, thereby nudging more economists to choose to include these in their models.¹²

Forming and Continuously Engaging a Stakeholder Advisory Board

Before a value assessment process begins, we recommend starting with the formation of a multistakeholder, patient-

centered advisory board that captures a variety of perspectives (eg, patients, caregivers, providers, payers, manufacturers, employers, and researchers). Stakeholder engagement, with an emphasis on patient engagement, is considered a foundational component of patient-centered outcomes research and, more specifically, meaningful patient engagement is recommended in the process of formal value assessment (health technology assessment bodies or value assessment frameworks) for a variety of reasons.¹³⁻¹⁶ The Patient-Centered Outcomes Research Institute (PCORI) considers stakeholder engagement a critical component of its merit-review process and guides applicants with a detailed rubric describing several engagement principles (reciprocal relationships, colearning, partnership, trust, transparency, and honesty).¹⁷

Would value assessment be better if we more intentionally capture commonly neglected elements of value?

Once the board is formed, the roles and responsibilities of the board must be made clear. The board should have and understand its governance role and it should be obvious that its role is not to be a “rubber stamp” for what the researchers decide to do. We also recommend a formal plan to continuously engage the board throughout the entire project life cycle to enable multiple points for gathering input, collecting feedback, and demonstrating a true partnership between the research team and board.^{7,17-19} Further, board members should be provided fair compensation for their time and the engagement strategy should be thoughtful of the time commitment expected of each member.^{16,17} When multistakeholder advisory boards are meaningfully engaged, iterative improvements throughout the project planning, execution, and dissemination phases can help increase the patient-centeredness of the assessment.²⁰⁻²² Having an advisory board does not guarantee a high level of engagement, but rather provides a mechanism for engagement to occur. It is still up to the research team to develop meeting agendas with ample time for discussion, deliberation, voting, and “open microphone” time to let board members share their perspectives. Take real queues from the board and allow them to truly guide the research agenda.¹⁹

Identifying, Synthesizing, and Utilizing Patient-Centered Outcomes in Economic Evaluations

Identification and planning

Following advisory board formation, a research agenda must be determined. A formalized process of topic solicitation enables advisory board and research team members to deliberate and approve projects. Articulating this process in a governance document improves the transparency of decision making for all participants. Research agendas can be driven by financial support or other sustainability considerations. Treating the advisory board as a true decision-making body requires open and honest communication about all factors that could influence topic selection.

Once multiple topics have been identified, different experts may be needed to provide subject matter consultation or may be used to help with the work itself. The Institute for Clinical and Economic Review (ICER), a US-based organization that conducts healthcare-related value assessment, reports its process to engage a variety of stakeholders at various levels—from formal advisors to contracting external experts—to conduct a large proportion of their work.²³ If you plan to contract out major components of the value assessment work, a standard set of methods may improve consistency and reproducibility. Additionally, when contracting external organizations to lead a component of the value assessment, it may be important to reiterate the importance of the patient-centered advisory board throughout the process. Why bother engaging a multistakeholder advisory board in the first place if the patient perspectives just get drowned out by external contractors who may not be committed to patient centricity?

After consultation with topic experts to assess the current scope of the project and information needs, presenting this new information will help the advisory board and research team prioritize topics and document patient and other stakeholder comments or concerns. This step is critical to demonstrate to everyone that the research team is committed to incorporating this feedback and, if gaps exist, those can be identified early in the process. There should also be opportunity for additional stakeholders to contribute their perspectives on an appropriate framework for a value assessment.²⁴

Synthesis and discovery

Synthesis and discovery should include not just systematically reviewing existing literature, but simultaneously beginning qualitative research to identify topics potentially missed in past research. Keep in mind that past literature is likely based on research that did not include patient engagement and can be biased toward inclusion of research questions and outcomes considered important to clinicians and researchers rather than patients. Thus, qualitative research with patients and caregivers will typically be needed. Evidence identified through published literature, interviews, and focus groups should be presented to the advisory board and potentially considered for poster or manuscript development.

With CEAs and value assessments relying on quantitative modeling techniques, gaps identified through literature review and qualitative research should inform new observational and/or experimental research. For example, if a disease typically imposes substantial burden on caregivers, but there are no relevant, existing cost-of-illness or health-utility elicitation studies with a focus on the caregiver, the research team may need to focus on filling these gaps before proceeding with the value assessment. Now, suggesting that health economists charged with building economic models are also responsible for conducting qualitative interviews, focus groups, or lead patient engagement activities might create additional problems without the proper training. The process of value assessment is, by

necessity, a multidisciplinary science. It is likely unreasonable to expect any single organization to be responsible for filling all of these research gaps prior to proceeding. But this gap analysis should be presented to the advisory board for a final determination of whether the research team should proceed with the value assessment with the missing data given the impact of that variable.

It should also be noted that using rigorous methods during the synthesis and discovery stage improves the likelihood of publishing findings in a peer-reviewed journal and helps build the case for future funding if any gaps are identified where additional research is needed. Communicating these gaps to major federal agencies (eg, PCORI, Agency for Healthcare Research and Quality, National Institutes of Health), patient advocacy organizations, or other groups with a potential interest (eg, industry, insurers, foundations) could raise awareness in a way that could lead to future funding opportunities for research.

Dissemination

As the body of evidence for patient-centered outcomes grows, the stakeholder advisory board's role is to help with reviewing and interpreting findings to assist to optimize communication and dissemination.^{13,18} Engaging patients and other stakeholders in the dissemination phase enables thoughtful consideration of the most appropriate channels for communicating results. Publication of patient-centered outcome evidence synthesized through systematic review or discovered through research in traditional academic journals should still be a priority so that results are peer reviewed and considered to have followed good methods practices. However, the dissemination should not stop at academic journals or professional meetings. The research team should go further to ensure that patients, policy makers, and the public at large are able to understand the findings.¹⁸ This might include drafting patient guides or specifically working with patient advocacy organizations or patient navigators to get the information out in a way that fits the audience.¹⁸

Future Directions and Recommendations

Make data available and easily accessible

To further increase the likelihood that the identified value elements will be incorporated into value assessments, a publicly available, centralized database should be created and maintained to improve ready access. The CEA Registry, created and maintained by Tufts Center for the Evaluation of Value and Risk in Health, provides a similar service through a process of systematically reviewing published CEAs and synthesizing article information, cost-effectiveness ratios, and utility weights reported, allowing for users to quickly identify variables useful for economic analyses.²⁵ Currently, PCORI also offers a searchable database of funded projects on its website but key patient-centered outcomes aren't extracted and synthesized in a user-friendly manner.²⁶ The PCORI infrastructure combined with our proposed process could make it much easier for value assessment developers to identify patient-centered outcomes

that have been curated in a way that is consistent with PCORI's own stated foundational elements required for patient-centered outcomes research.¹³

Assess quality of data

Posting a set of patient-centered outcomes to a searchable database could improve the efficiency of value assessment development, but the job would not be complete without further context around the evidence used to support those outcomes. Any elements identified and quantitative variables posted should include some assessment of quality of the data and an assessment of the risk of bias when using the element in a value assessment. While no theory of evidence synthesis for inputs in a CEA currently exist, other standards for evidence rating and quality of evidence for recommendations in healthcare could serve as a template to guide how we consider existing patient-centered outcomes.^{10,27} Providing some context around the quality of evidence available would help value assessment researchers consider the level of uncertainty for different components of their models and consider different sensitivity and scenario analyses to address.^{28,29}

Commit to transparency

While methods and model transparency have been recommended and advocated for in health economics for many years, simply having access to programming code and value assessment inputs is not enough.³⁰ ISPOR and the Society for Medical Decision Making Good Research Practices in Modeling Task Force described transparency in the economic modeling context as "the extent to which interested parties can review a model's structure, equations, parameter values, and assumptions" with the intention "to provide sufficient information to enable the full spectrum of readers to understand a model's accuracy."³⁰ While publishing CEA protocols or making models publicly available in a repository could address transparency and accountability in the health economics research community, these steps may not improve the transparency to the patient community or general public.^{7,10,31,32} Emerging practices such as providing nontechnical documentation, cataloging questions and concerns, documenting how concerns will be addressed, and providing updates can help improve the level of transparency for patient communities.¹⁶ We also recommend specifically highlighting patient-centered outcome considerations in results tables and presenting these to the advisory board for confirmation.

Conclusion

When significant evidence gaps exist, it is not enough to simply throw these flaws into the abyss of limitations and sensitivity analyses. Value assessment researchers should engage a broad community of stakeholders early and often, with an emphasis on the patient, and seek to fill these gaps. Health economists should not be expected to go down this path alone, but in collaboration with different disciplines with the skills needed. •

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Evolution of Precision Medicine: Applying a Population-Based Evidence Assessment Repository to Achieve Patient-Centered Outcomes at the Point of Care

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SUMMARY

The authors propose a framework that shapes goals based on patient values and shared decision making that is continuously refined by utilizing a population-based evidence assessment repository to achieve personalized care. While the framework described will be more easily implemented in an outpatient clinic for chronic disease treatment, components could be applied to inpatient settings depending on the scenario. As more discussion and information are completed and population-derived value assessment evidence is applied, the treatment options are reduced to the most effective for the particular patient. Treatment options tailored towards the patient's needs would be guided by the clinician's acumen and the evidence. It would also allow the discussion to proceed based on population-based value endpoints that were then tuned based on the individual's characteristics and wishes.

Introduction

Patient-centered care entails delivering clinical services that incorporate individual patient preferences, concerns, and needs. It ensures that values of the patient inform all treatment decisions. Patient-centered care comprises a central component of recommendations on improving the US healthcare system in the National Academy of Medicine (formerly the Institute of Medicine) seminal consensus report, "Crossing the Quality Chasm." The goal of patient-centered care is to empower patients to be informed decision makers by providing whole-person care that is both compassionate and empathetic.¹ Improvements in clinical endpoints, as well as increases in patient engagement and self-management, have been demonstrated in studies examining the impact of patient-centered care.^{2,3}

Equal in importance to incorporating the spectrum of patient preferences in the treatment paradigm is the necessity to consider evidence that is enriched by broader, diverse study populations with analytic endpoints that are valued from the patient perspective. Juxtaposed to traditional randomized, clinical trial (RCT) data, population-based evidence sourced from real-world settings has been described as potentially more relevant, adaptable, efficient, diverse, and generalizable than RCTs. Given that traditional RCTs are generally constrained to highly specified treatment protocols for measurement of efficacy in narrow populations, large population-based, real-world studies may offer even more rich, diverse, and informative findings of how a treatment intervention will be expected to perform in actual clinical settings.⁴

To improve healthcare quality indicators in the United States, 2 activities must ensue. First, we must incorporate patient preferences in treatment considerations. Second, we must better apply population-based value assessments in formation of the patient care plan. To achieve the massive improvement

that would move the United States closer to peer-developed nations for quality indicators, both activities must be coordinated with each other at the point of care for synergies to occur. Effectively coordinated, the process could transform healthcare by empowering patients, reducing uncertainty in clinical decision making, building efficiencies in the treatment selection process, and improving outcomes.

The goal of patient-centered care is to empower patients to be informed decision makers by providing whole-person care that is both compassionate and empathetic.

Strengthening patient-centered care and achieving evidence-based outcomes entail bolstered application of population-derived value assessments at each step of the point-of-care visit and in follow-up care. Moreover, the massive shift to telehealth services during the COVID-19 pandemic has brought to light new challenges and new opportunities for utilizing technology to enhance patient-centered care.⁵ Many of these measures will likely remain after pandemic control is attained. The ability to receive additional patient-relevant information using web-based interfaces and increased adoption of secure video conference applications (eg, Zoom, Skype, Google Meet, Microsoft Teams) that facilitate sharing of important details can improve the experience for the clinician and the patient. This knowledge transmission will ultimately strengthen quality of care.

We propose a framework that shapes goals based on patient values and shared decision making that is continuously refined by utilizing a population-based evidence assessment repository (PEAR) to achieve personalized care. While the framework we describe will be more easily implemented in an outpatient clinic

for chronic disease treatment, components could be applied to inpatient settings, depending on the scenario. As more discussion and information are completed and population-derived value assessment evidence is applied, the treatment options are reduced to the most effective for the particular patient (Figure 1). Treatment options tailored towards the patient’s needs would be guided by the clinician’s acumen and the evidence. It would also allow the discussion to proceed based on population-based value endpoints that were then tuned based on the individual’s characteristics and wishes.

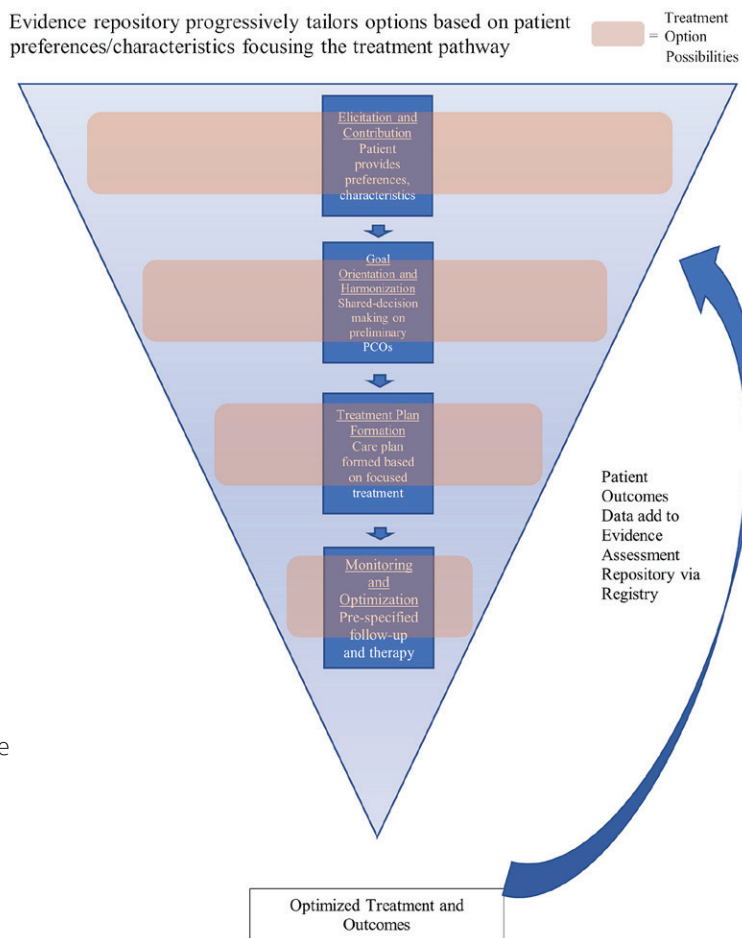
Step 1: Elicitation and Contribution

The first step we call “Elicitation and Contribution” is performed by the patient prior to the visit via internet or at patient intake via a patient portal. It involves the patient summarizing their reason for the visit to the extent possible (“elicitation”) and provides fields for the patient to “contribute” key information on their preferences, as well as social determinants, that may influence the outcomes and affect relevance of potential treatment options. As described earlier, the framework most lends itself to outpatient care where the patient has the flexibility to provide thoughtful input regarding their preferences. Along with the patient reporting the reason or chief complaint, they will describe the individual goals for the visit and the treatment plan in a text-fillable form that can aid the clinician in crafting a care plan. While many patients will report a simple short response (eg, “I want my cough to stop as soon as possible”), other patient situations would benefit from providing a more textured response (eg, “I’ve had right knee pain and my goal is to lower the pain so I can keep gardening”). This would likely entail a different treatment plan than “I’ve had right knee pain and my goal is to keep mountain climbing, so I can climb next month.” If the visit was a routine follow-up visit, there would be a reduced amount of new details in this first step of the visit. However, Step 1 still provides a structured opportunity for the patient to describe their visit goals based on their perception of their current health state.

Similar to travel agency or hotel booking websites that allow filters to be applied, the web portal would be accessible by computer, smart device, or kiosk at the point of care. It would feature a graphical user interface to capture their preferences via touch-sensitive icons, sliders, and text fields (low cost, noninjectable, side effect profile, once-daily, gender, ethnicity of provider, language). This would be stored in the electronic health record for review by the provider and the medical team at any point.

The evidence on the profound influence of social determinants of health on treatment outcomes continues to increase.^{6,7} While not directly causative, presence of certain demographic, social structural, and attitudinal belief factors are correlated with health services utilization.⁸ The proposed framework would factor in social determinants to discern options that are likely to be effective given the patient’s characteristics. The PEAR includes relevant comparative value assessments such as the

Figure 1. Population-based evidence assessment repository (PEAR) triangle.



National Institute for Health and Care Excellence technology appraisals and the Institute for Clinical and Economic Review assessments, and would begin sifting the evidence based on the patient’s needs, preferences, and characteristics.^{9,10} Based on the patient responses, the PEAR would produce an initial broad array of potential therapy options. While the clinician and the patient have yet to determine if treatment will be pursued, possible therapeutic approaches begin to materialize as options. This sets the stage for treatment to be tailored based on study type and populations in the literature to ensure relevance to the specific patient (eg, comparative effectiveness data sourced from an observational study that included older adult minorities).

Step 2: Goal Orientation and Harmonization

At the point the clinician determines that treatment is feasible and medication could remediate symptoms, the second step, “Goal Orientation and Harmonization,” occurs. Research in the field of health behavior theory has illuminated the importance of understanding the patient’s motivations and beliefs to energize behavior changes. This clarifies that patients are much more likely to adopt a behavior, embark on a treatment, or complete a treatment if the care process was commensurate with their beliefs and is consistent with their values regarding aspects such

as cost, convenience, pain, and embarrassment. The objective is to “meet the patients where they are” to activate participation and performance in their own care.¹¹

The second step involves the intentional process of determining the patient’s goals of treatment via discussion with the clinician to map to the patient-centered outcomes that are salient (“orientation”). The clinician would be supported by the PEAR to elucidate the patient-centered outcomes that are most likely to be achieved. This would foster the shared decision making needed to finalize the goals of the current care plan (“harmonization”). Incorporating the patient’s preferences and honoring the patient’s background would distill goals based on his or her priorities that were supported by evidence. The PEAR has again focused the relevant therapy options based on the goal selection.

Assuring the patient that it is a “safe space” for them to express their concerns, needs, and beliefs is fundamental to success.

Discussing with the patient what they would like to achieve also demands level-setting on what is reasonably attainable. For example, if a patient seeks treatment after a hip fracture hospitalization and the bone-mineral density scan reveals the patient is severely osteoporotic based on a t-score of -2.5, it would be unrealistic for the patient to target a normal bone-mineral density within 1 month. The PEAR would provide outcomes information that offers an array of potential outcomes based on the patient’s characteristics and evaluation that would show the horizon of possible patient-centered outcomes and the comparative-effectiveness research studies that inform the patient and clinician on what the expected benefit could be and the uncertainty around that estimate.

This would be displayed to the clinician on the screen of a tablet or the computer in the consultation area directly from the electronic health record. The patient and the clinician would walk through the displayed outcomes from the PEAR. This would show the outcomes achieved from the possible treatments textured by the study population and type of study.

Step 3: Treatment Plan Formation

The third step is “**Treatment Plan Formation.**” Clinical studies are increasingly focusing on reducing medication use via trial and error approaches towards evidence-driven prescribing.^{12,13} To reduce uncertainty, the evidence repository would display options with the probability of success, based on the patient-centered outcomes goals laid out in Step 2 that incorporate patient preferences and characteristics elicited in Step 1. This would distill a rational pathway of initial treatments and alternative medications. This would clarify treatment options relevant to the specific patient. The evidence repository would also make clear difficulties around dosing,

administration challenges (eg, need for storage upright and shaking prior to injection), and delivery complexities (eg, risk evaluation and mitigation programs, specialty pharmacy dispensing, required monitoring) that should be considered. For example, a patient with diabetes interested in reducing her hemoglobin A1C (HgbA1c) would be able to view a display of the potential medication categories that would provide their relative effectiveness averaged by group. This would allow comparison for GLP-1 agonists compared to oral DPP-4 inhibitors. Clicking on the categories would then show the within-group medications compared to each other. Medication such as a GLP-1 agonist would display its relative improvement in achieving HgbA1c compared to others within the category. The options would be perpetually filtered and reappraised based on patient preferences gleaned through the steps of the framework including benefit, patient ability to pay, complexity in administration, or dosing time. In terms of the value-based assessments, those could also be tailored based on patient preference. If the patient was only interested in medications that had demonstrated a mortality benefit, the evidence dossier would reduce to those studies and the affiliated medications. This would work similar to moving from different forest plots in a meta-analysis from the aggregated point estimate to the subgroup estimate. While the options would be prefiltered based on the information entered during Elicitation and Contribution, the system is flexible such that patient and provider could always modify the information as the discussion ensued with the PEAR responding by modifying the options.

Step 4: Monitoring and Optimization

The fourth step is “**Monitoring and Optimization.**” Many patients require more than 1 medication to achieve chronic disease control (eg, hypertension, diabetes) with these doses titrated to achieve maximum efficacy. “Monitoring” involves deliberate planning for follow-up based on the evidence. Effectively the treatment plan follows a longitudinal model of continuous improvement based on the follow-up findings. For example, if the treatment plan for a patient involves use of an antidepressant for improvement in depression based on improvement on the Hamilton Depression Rating Scale, then a formalized plan for follow-up visits would be scheduled based on the data regarding when the medication effect would be stabilized.¹⁴ The follow-up visit would also occur based on additional evidence including pharmacokinetic studies that inform best approaches to titrate the dose for improved effect or mitigation of side effects. As monitoring proceeds, the clinician is informed by the evidence assessment repository on data-driven steps to adjust the treatment to yield highest probability of achieving the patient-centered outcomes (“optimization”).

Patient-Centered Outcomes Experience Feeds Into a Patient Registry

The systematic longitudinal care plan guided by the evidence also provides a mechanism for the patient data to contribute to registry data that will add to evidence base. The prespecified

measurement of the evidence-driven decisions and the resulting outcomes will contribute to a patient registry. This allows the framework to not only optimize care at the patient level, but also contribute to the real-world data population. This registry could then serve as a data set for studies that will contribute estimates in the PEAR at a later point. The framework not only leads to improved care for the patient receiving care but will also be harnessed to improve the quality of the real-world data.

Right Sizing the Program

Not all care settings will have the resources to accomplish all facets of the model described. Hence, evaluation will be needed of the capabilities of the clinical setting to evaluate the patient and their preferences. If care is provided at a small, rural clinic, a scaled-down application of the model would be performed. Elicitation and contribution could still be completed at or before intake. However, internet broadband capabilities may limit the ability to fully utilize the PEAR for goal orientation and harmonization. Even in this circumstance, treatment plan formation can apply the information garnered from the Elicitation and Contribution steps based on smart phone-based medication applications that detail FDA-approved outcomes. Monitoring and optimization would proceed by less technologically intensive operations. Simple discussion and mapping out of the follow-up visits, predicated on times when effect would be reached, would still allow for titration to proceed in an organized manner. Without the aid of the full population-based evidence assessment repository to guide this process based on the relevant evidence, the process is expected to involve more “trial and error” to achieve optimal medication and dose. However, consistently applying the process will facilitate improvement as technology or capacity improves in availability for clinics that are currently under resourced.

Deploying the Program

Training of clinicians would be an important first step to ensure understanding of the goal to wholly incorporate patient

preferences in the process of selection of goals and treatment decisions. The model involves perpetual review of the data at each step to reshape the care plan. This refines the treatment plan based on the particular needs and wishes of the patient. A medication that is efficacious for treating high blood pressure but is associated with frequent urination in a patient who has difficulty ambulating to a bathroom on a different floor of the house would not be a wise treatment option. Ensuring that clinicians understand the overall motivation and fully appreciate the benefits from the patient perspective will be an important component of ensuring the framework functions as intended.

Incentivizing patients to participate in this new process will be achieved by clearly messaging the goal to provide better care that meets their specific needs. There will also be a diversity in patient motivation to participate in this novel care experience. Patients may be resistant, at first, to this process of eliciting their preferences, beliefs, and characteristics. Assuring the patient that it is a “safe space” for them to express their concerns, needs, and beliefs is fundamental to success.

The framework will require computational infrastructure to support the PEAR and clinician training on how to operationalize the system. Support from health information technology organizations will be a necessary component both prior to deployment and after.

Conclusion

We see this stepwise, evidence-driven, patient-centered model as the evolution of precision medicine in which therapeutic treatment is tailored beyond tissue or receptor types to therapy based on the patients’ preferences, characteristics, and their complete health state. While initial training and infrastructure are the tradeoff, the net gains in terms of improved outcomes, empathetic care, patient engagement, and operationalization of rapidly growing population-based data would easily offset the investment. •

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Coproduction in Learning Healthcare Systems Is the Key to Unlocking True Healthcare Value

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SUMMARY

In the Epilepsy Learning Healthcare System, people with epilepsy and their care partners, community organizations, clinicians, researchers, and health system leaders work together. They design, implement, and share the results of collaborative research and quality improvement efforts, leading to better health outcomes and increased quality, experience, and value in care. In this article, the Epilepsy Learning Healthcare System demonstrates how coproduction can dramatically accelerate the ability to generate new knowledge and put it into practice from its work in planning the creation, validation, and implementation of a health-related quality of life for rare epilepsy populations.

What Is True Healthcare Value?

Value in healthcare has been defined as “quality of care ÷ costs,” with several components of quality that include clinical outcomes and the patient experience. Perhaps the important question about this definition is, “who determines what is an important outcome?” If the decision doesn’t incorporate the perspectives of the person with the condition and their care partners (if needed) into criteria for outcomes, the value equation fails to protect the interests of the most vulnerable of stakeholders in the healthcare complex: the patient.

Patient-centered care has emerged as a dominant care philosophy placing the patient and family at the center of all decisions. Traditional healthcare models relied on the expertise of physicians to make appropriate decisions about diagnosis and treatment of their patients. “Shared decision making” is a means of incorporating patient preference and is an improvement towards patient-centered care. However, a limitation of the typical model is that shared decision making occurs at the treatment decision and doesn’t incorporate patient input into which outcomes are prioritized.

Likewise, the value-based approach to care has not yet incorporated “patient-centered” outcomes. In large part, the elements of the value equation are currently payer focused rather than patient focused. Incorporating patient preferences and priorities into the selection of outcome measures—both in clinical trials and in real-world evaluations of care—will better align the value equation with the philosophy of patient-centered care.¹

How Can Patient Preferences and Priorities Be Integrated Into the Development and Delivery of Improved Care?

The answer to this question is “coproduction.” Coproduction is a process of working together among people with epilepsy, care partners, healthcare providers, and community service providers to design a health system that optimizes the health outcomes that are most important to the affected person, in addition to

recognizing the resources required. Coproduction means being involved in decision making about which outcomes are to be improved. Coproduction ensures the patient will have options presented that are most relevant from their perspective.

An example of meaningful coproduction comes from our experience in designing a learning healthcare system for people with the epilepsies. In 2019, the Epilepsy Foundation worked with multiple partners to launch the Epilepsy Learning Healthcare System (ELHS) to improve the quality of care and outcomes for people of all ages diagnosed with one of the epilepsies. Learning healthcare systems ensure that clinical care, science, informatics, incentives, and culture are aligned for continuous improvement, innovation, and research.²

A limitation of the typical model is that shared decision making occurs at the treatment decision and doesn’t incorporate patient input into which outcomes are prioritized.

The epilepsies affect 1.2% of the population.³ Arriving at the correct epilepsy diagnosis is sometimes a complex process, often requiring extensive history, electroencephalogram monitoring, neuroimaging, and other diagnostic testing. Most forms of epilepsy require long-term follow-up and expensive treatments. Adverse effects of therapy are common and impair quality of life (QoL). Epilepsy is associated with high rates of comorbidities (eg, depression, anxiety, cognitive deficits) and excess premature mortality (eg, accidents, sudden unexpected death in epilepsy, suicide). Health disparities in epilepsy outcomes have been identified, driven in part by social determinants of health.⁴ Direct costs (medications, testing, emergency room visits, hospitalizations) and indirect costs (under/unemployment, lost productivity of patients, and caregivers) are high.⁵ Despite the clear negative impact

of epilepsy on both QoL and health costs, few studies have addressed the value of epilepsy care, especially studies with purposeful inclusion of patient perspectives on value. In treatment trials for the epilepsies, the primary clinical outcome measure is nearly always a measure of seizure control,²⁻⁶ operationalized as a 50% responder rate (eg, the percent of participants who had a 50% or more reduction in seizure frequency). Reductions in seizure frequency of this size have been traditionally accepted as a clinically meaningful difference in outcome, regardless of the specific population for the indication. However, rare epilepsies are characterized by much more frequent seizures, in which a 50% reduction in seizures could be of limited clinical significance. Counting seizures provides a quantitative measure of an intervention's impact, which is a critical consideration for regulatory approval.

However, while seizures are the defining feature of the epilepsies, the broad spectrum of developmental impacts, QoL, comorbid conditions, and adverse effects of treatment are cited by patient and family partners (PFPs) as much as, or more important than, the number of seizures remaining.^{6,7} For example, extensive international consultation with patients with Dravet syndrome and their caregivers has found that across cultures, families and patients have identified seizures as an important outcome, but view as equal impacts of the condition the effects on motor skills, expressive and receptive communication, learning, attention, emotional well-being, community functioning, daily activities, and sleep.^{8,9} Similar themes have been reported by parents of children with other severe early life epilepsies.⁶ Measures of seizure frequency or severity alone do not capture the totality of experience for children or families living with the rare epilepsies. Clearly, evaluations of value in epilepsy must go beyond the number of seizures to incorporate more global measures of functional impact that are meaningful to patients.

Integrating Patient-Centered Outcomes in ELHS

In ELHS, we seek to coproduce the improvement objectives with patient and family partners who represent the diverse spectrum of people affected by the epilepsies. The unanimous message from PFPs was that measures of QoL were equally or more important than seizure frequency, which had been the measure prioritized by clinicians and researchers earlier in the process. Without this coproduction process, ELHS would have failed to appropriately prioritize an outcome that mattered as much as seizure control from the view of patients and families.

In addition, we needed to identify reliable methods to measure QoL for everyone in our diverse population. Existing validated QoL scales, such as the PROMIS measures and the epilepsy-specific Quality of Life in Epilepsy-10 (QOLIE-10), can be employed with neurotypical adults and adolescents, and the Epilepsy-PedsQL can be used with neurotypical children (or children and adults who are severely developmentally delayed, as often occurs in many rare epilepsy syndromes); however, there are no validated scales that appropriately measure QoL.

The QOLIE-10 was developed to serve as a brief survey of health-related QoL (HRQoL) for adults with epilepsy. Ten questions are completed by the person who has epilepsy. The QOLIE-10 covers general and epilepsy-specific domains grouped into (1) epilepsy effects (memory, physical effects, and mental effects of medication), (2) mental health (energy, depression, overall QoL), and (3) role functioning (seizure worry, work, driving, social limits).¹⁰ The QOLIE-10 can be completed by a patient and reviewed by the physician within the timeframe of a visit. The scoring rubric allows for different weights to be attributed to different domains according to the patient's individual prioritization of those domains.

For neurotypical children, youth, and young adults (2-25 years), the PedsQL-Epilepsy Module provides a validated measure of HRQoL that can be used in the clinic. The PedsQL Epilepsy Module is a 29-item measure with 5 subscales (ie, impact, cognitive, sleep, executive functioning, and mood/behavior) with parallel child and caregiver reports.¹¹ However, the development and validation samples for the PedsQL Epilepsy Module included only a small portion of individuals with rare epilepsies and intellectual disability, precluding differentiation of items and subgroup analyses for intellectual disability.

Coproduction is the answer to the question, "how do we unlock true value in healthcare?"

For children and adults who are severely developmentally delayed, we are actively collaborating with international experts in QoL in relation to intellectual disability¹² and epilepsy¹¹ to develop and validate such a HRQoL scale for this most vulnerable population. This will be the first measure that can be used across the developmental spectrum (from 2-40 years of age) with parallel self- and caregiver proxy reports for patients with rare or severe epilepsies. The need for a caregiver report is especially important when children are too young or cognitively unable to complete measures, and for older individuals who are unable to complete questionnaires. We will use a coproduction approach across ELHS, rare epilepsy patient organizations (collectively known as the Rare Epilepsy Network), and industry partners and regulators (members of the Research Roundtable in Epilepsy) to collaboratively develop a PedsQL Rare Epilepsy Module. This innovative approach will require coordinated engagement and interaction between a consortium of every stakeholder group (ie, rare patients and families, rare epilepsy organizations, clinical trialists and healthcare providers, experts in outcome assessment, drug and device company sponsors, and regulators).

We will identify items for inclusion in a rare epilepsy HRQoL instrument by conducting extensive interviews with caregivers and affected individuals; confirm content validity using cognitive interviewing techniques and consulting with expert consortium members; and field test the HRQoL instrument with ~250 to 300

individuals ages 2 to 40 years with rare epilepsies and/or their caregivers, thereafter, conducting psychometric evaluations. We hypothesize that evaluation will yield a robust measure of HRQoL including internally consistent factors, the ability to detect differences between important clinical groups (eg, motor abilities, seizure severity, presence of comorbidities), and sensitive and reliable minimally clinically important difference values and clinical cut-off scores. Our work in this area will validate a measure for epilepsy-specific HRQoL for future clinical trials and clinical assessments of value of therapeutics to reduce severe and treatment-resistant epilepsy in a population for whom a validated HRQoL is not yet available.

Conclusion

In conclusion, we propose that integrating the appropriate QoL assessment into the standard of care for the epilepsies through improvement methodology will unlock true value in ELHS. Value assessment in a learning healthcare system that uses

outcome measures that were identified by patient and family partners and ensures that those measures are both appropriate for the populations to be assessed and (ideally) individually weighted toward the patient/family partners, preferences for outcome becomes a truly “patient-centered value assessment” methodology. Such patient-centered assessments, whether carried out during clinical development as part of clinical trial endpoints or during clinical management/treatment decisions to improve the true value of epilepsy care, are sensitive to patient priorities in a way that seizure frequency outcomes alone are not.

We believe that coproduction, embedded within a learning healthcare system framework, is an essential and innovative approach to consistently and reliably incorporate patient-centered outcomes in health decision making and assessment of value. Coproduction is the answer to the question, “how do we unlock true value in healthcare?” •

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