

Amplifying Patient- & Caregiver-Centered Value in Rare Disease Treatment

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INTRODUCTION

Background

The advancement of healthcare technology has resulted in immense societal benefit, most recently exemplified by the rapid development of COVID-19 vaccines, transforming health at both the population and individual levels. Understanding the value of these health technologies is increasingly important as healthcare costs rise and as both public and private payers across the globe are charged with being good stewards of finite healthcare dollars. The systematic evaluation of a health technology and the impact it has on individuals and populations with a given clinical condition is conducted through a process called a health technology assessment (HTA). The World Health Organization (WHO) describes HTAs as “a bridge that connects the world of research to that of policy making” and explains that they “can be used by decision makers and other stakeholders to support the decision-making process in health care at the policy level by providing evidence about given technologies” (WHO, 2022). Depending on the intended audience and purpose of a given HTA, a “value framework” will be selected to guide the assessment. Value frameworks represent the approach used to measure the value of the technology being assessed, outlining the methods, criteria, and evidence types to be used.

Historically, HTAs have been conducted using traditional value frameworks that rely on measures of clinical benefit from clinical trial data, health-related quality-of-life estimates, healthcare utilization projections, and efficiency metrics applied to standardized patient populations. While this approach has a significant advantage in feasibility, recent focus on disparities in access and outcomes indicate a need for a more holistic, patient-centered approach for defining value. For patients living with one of the more than 7,000 known rare diseases (About Rare Diseases, 2012), where indirect, non-medical burdens comprise more than half of the total disease burden (Yang, 2022), traditional HTAs fall short in accounting for the ways a therapy addresses the total burden of illness experienced by affected individuals (Nestler-Parr S., 2018). Many rare diseases are chronic, progressive, and without a cure, leaving patients to face annualized costs up to ten times higher than more common conditions (Lakdawalla DN D. J., 2018). The limited research available often focuses on “hard” efficacy endpoints needed for regulatory approval, leaving an evidence gap for the condition’s total impact on patients, their families, and caregivers. This gap is particularly pronounced for those who are affected by the vast constellation of symptoms associated with rare demyelinating neurologic disorders. For example, research findings for “snowflake diseases” like generalized myasthenia gravis (gMG) are not often generalizable due to a high degree of symptom variability, compromising the ability for traditional HTAs to assess overall treatment benefits (MGFA, 2022).





In this white paper we present a case for reconsidering how to define “value” for technologies in rare diseases such as gMG and for incorporating patient-centered value into HTAs through patient-centered value frameworks.

MEASURING VALUE

Traditional HTAs

Prior studies have indicated a disconnect between provider perceptions and patient perceptions of treatment goals and measures of success, reinforcing that the definition of value varies by audience (e.g., policymakers, value assessors, patients, providers) (Shafrin J, 2017). This presents an opportunity to more closely align on standardized metrics of value that encapsulate a greater cross-section of components—particularly those that are deemed important by patients and their caregivers. Safety and efficacy endpoints used in rare disease clinical trials are designed to assess whether the treatment is effective with the goal of bringing treatments to patients quickly. These endpoints are necessary but not sufficient, as they can lead to an undervaluing of the patient burden and the exclusion of caregiver and family burden. Traditional value frameworks also vary in the level of specificity for studied impacts (e.g., quality of life vs. activities of daily living (ADL)) and this inconsistency in definitions presents a challenge for comparing value across frameworks. Further, as noted earlier, the available evidence upon which the model assumptions are built are not generalizable to heterogeneous populations within the rare disease community.

Unique Challenges for Rare Diseases

When the economic impacts of a disease are defined by direct care costs, the burden of indirect costs such as lost career opportunities, workforce absenteeism, unpaid time off, need for additional childcare, or need for paid caregiving are left unaccounted. Yet many of these cost burdens disproportionately fall on the patient, not the healthcare system.

Value seen through the lens of healthcare costs and utilization neglects the impact of the disease burden on patients and their loved ones in their day-to-day life and the tradeoffs they face. For example, Avalere’s ongoing research suggests that the toll of occupational, financial, psychosocial, and other burdens has a substantial impact on patients and caregivers affected by gMG. A recent review of evaluations by the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) revealed that rare disease therapies evaluated with the standard Single Technology Assessment—which is designed to evaluate treatments targeting large eligible populations—were disadvantaged in the marketplace (i.e., approved less frequently or requiring multiple reviews) compared to those assessed by Highly Specialised Technology evaluations, which allow a higher cost threshold but are only used under strict criteria for treatments in extremely rare conditions (Clarke, 2021). Without a tailored HTA methodology for rare diseases, HTA bodies rely on decision-making criteria that may discount the unique challenges in developing therapies for these conditions and may make those decisions without robust data to demonstrate a treatment’s patient-centered benefit. Patients, payers, and employers all stand to benefit from a fit-for-purpose, evidence-based approach to value assessment that accelerates appropriate access to life-altering therapies and technology.





UNMET NEEDS FOR EVALUATING RARE DISEASE TREATMENTS

A targeted review of existing value frameworks (and those under development) identified two areas of weakness that impede creation of holistic assessments of value for rare disease treatments—particularly those that predominantly confer morbidity benefits. First, there is a paucity of research to understand the lived experience for different diseases and how heterogeneity in disease experience and severity levels impacts willingness-to-pay thresholds. Second, there is a shortage of metrics that quantify patient- and family-centered impacts. Addressing these two foundational needs is imperative for the widespread development and adoption of patient-centric value frameworks and HTAs.

A more comprehensive view of assessing rare disease impact would encompass indirect burdens, such as opportunity costs, productivity loss metrics, family and caregiver impacts, health equity, severity of disease, and value of hope. These indirect burdens also impact overall healthcare costs along with patients' and caregivers' ability to fully participate in the workforce, both of which are important to payers and employers. Collectively these measures could assist with appropriate incentives for encouraging future research to develop treatments, inspire hope among patients and their loved ones and provide payers with the insights needed to make coverage decisions grounded in a holistic understanding of a treatment's value.

For example, while the commonly used MG-ADL tool can assess patients' ability to perform activities of daily living, it would require additional research and data capture to understand how those ADL limitations impact patients' social and mental health. Psychosocial impacts for both patients and caregivers are often neglected, though there is a known and significant mental health and emotional burden associated with disabling diseases (e.g., social isolation, self-esteem, fear, and loss of autonomy) (Spencer-Tansley R, 2022) (Boettcher J., 2020), which comes with its own negative effect on healthcare costs and workforce participation (National Safety Council, 2021).

HOLISTIC PATIENT-CENTRIC MODELS

With the limitations of traditional value assessment frameworks, new value frameworks are being introduced that address some of these limitations by adopting more patient-centric concepts. The last decade has ushered in these new conceptual frameworks, which we refer to as "patient-centric" frameworks, that incorporate additional variables more directly tied to overall societal benefit and the patient's perspective (e.g., equity, cultural barriers, societal spillovers, value of hope, and fear of contagion or disease). Examples of these models include:

- **ISPOR Value Flower** introduces eight potentially novel impacts, including reduction in uncertainty, fear of contagion, insurance value, severity of disease, value of hope, real option value, equity, and scientific spillovers (Lakdawalla DN D. J., 2018).
- **GRACE**, or the Generalized Risk-Adjusted Cost-Effectiveness approach, re-examines traditional cost-effectiveness thresholds to account for health-related quality-of-life differences between more severe diseases and milder diseases (Lakdawalla DN P. C., 2021).





- **PAVE**, or Patient-Driven Values in Healthcare Evaluation model, classified 42 patient-informed value elements into five domains (short- and long-term effects of treatment, treatment access, cost, life impact, and social impact) and 11 categories (tolerability, disease burden, forecasting, accessibility of care/treatment, healthcare service delivery, cost incurred on the patient, cost incurred on the family, personal well-being, stigma, social well-being, and personal values) (dosReis S, 2020).
- **IVI**, or the Innovation and Value Initiative, aspires to advance the science, practice, and use of patient-centered value assessment to support decisions that make healthcare more meaningful and equitable. The IVI identified six attributes that are important to individuals with major depressive disorder: mode of treatment, time to treatment effect, days of hopefulness, effect on productivity, relations with others, and out-of-pocket costs (IVI, 2021).
- **PC-CIS**, or the Patient-Centered Core Impact Sets, are intended to be patient-prioritized lists of disease and treatment impacts. The National Health Council convened a multi-stakeholder group to create a blueprint and toolkit for patient communities to develop PC-CIS for specific diseases (Schoch, 2022).

The domains and value elements used to capture the value of health technologies are shown in Figure 1, with elements in blue indicating those not currently considered by traditional HTA frameworks. In practice, including these elements in HTAs is not without challenges. Perhaps the biggest challenge is that measuring these elements requires well-developed and defined patient-reported and caregiver-reported measures. Both a perceived lack of rigor for qualitative data and the effort required to collect it hampers the acceptance of novel variables. This underscores the importance of validated, patient-centered outcomes assessment instruments, use of technology to automate patient and caregiver data collection, and rigorous research design and procedures (Huls SPI, 2019).



Figure 1. Avalere Summary of Value Elements Currently Considered in Value Frameworks

Domain	Holistic Approach to Value Elements		
Short- and Long-Term Treatment Effects	Tolerability <ul style="list-style-type: none"> Medication frequency Length of treatment Discontinuation Side effects (e.g., corticosteroid, immunosuppressive) Mortality 	Disease Burden <ul style="list-style-type: none"> Age of onset Intermediate / surrogate outcomes Remission Activities of daily living Symptom Importance 	Forecasting <ul style="list-style-type: none"> Impact on education Impact on career Inability to plan Life expectancy Disease severity Predictable healthcare needs Untreated illness severity
Treatment Access	Accessibility of Care/Treatment <ul style="list-style-type: none"> New therapeutic option Available treatment Provider willing to deliver care Proximity to care location System navigation 	Healthcare Service Delivery <ul style="list-style-type: none"> Explanation of treatment (risk & benefits) Provider relationship and trust Care transitions Consistency of care 	Other <ul style="list-style-type: none"> Value of knowing Real option value
Treatment Costs	Cost Incurred by the Patient <ul style="list-style-type: none"> Direct medical costs Cost of treatment-related side effects Long-term costs Reimbursed care Affordability 	Cost Incurred by the Family <ul style="list-style-type: none"> Long-term effects on the family Relocation costs Autonomy / dependence 	Other <ul style="list-style-type: none"> Transportation costs Insurance value: financial & health
Life Impact	Personal Well-Being <ul style="list-style-type: none"> Fatigue Ability to work / Productivity Physical abilities Emotional status / mental health Lost or delayed childbearing 	Stigma <ul style="list-style-type: none"> Embarrassment / Self-Consciousness Rejection by family Rejection by society 	Other <ul style="list-style-type: none"> Lower workforce participation Missed work / time for treatment & hospitalization Presenteeism Fear of contagion / disease Value of hope Diminishing returns to QoL
Social Impact / Other	Social Well-Being <ul style="list-style-type: none"> Support network Relationship with family Relationship with peers Maintaining social activities 	Personal Values <ul style="list-style-type: none"> Cultural barriers Religious beliefs 	Other <ul style="list-style-type: none"> Symptoms (experienced by patient) Signs (observed by patient / others) Scientific spillovers Equity

■ PAVE, NHC, IVI, GRACE
 ■ Traditional Framework

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gMG: A CASE EXAMPLE

gMG is a rare, neuromuscular autoimmune disease characterized by muscle weakness and fatigue resulting in functional impairment and affects respiration, mobility, vision, and speech (Atkins, 2021). The prevalence is estimated at 27.8 per 100,000 individuals and disproportionately impacts women (54%–66%) (Fang F, 2015). Although Black women have a higher incidence rate, other aspects of racial differences are poorly understood due to limited gMG research and generalizable patient sampling (Alskehlee A, 2009). Uncontrolled gMG impacts patients’ ability to perform ADLs. There is no cure, and as symptoms progress, many individuals with gMG can no longer live their lives without the help of others, maintain full-time employment, or carry out their day-to-day lives without significant limitations from the disease. Most patients remain on chronic immunosuppression maintenance therapies for the rest of their lives.





Accessing those therapies is of particular concern in gMG, as arriving at a therapeutic regimen that works and obtaining that therapy is a long process for many patients. The small number of neurologists who have experience and expertise with gMG are usually concentrated near academic medical centers or in urban areas, meaning that patients must either navigate frequent travel or outright relocation, a burden of disease in and of itself. They may face insurance coverage barriers and financial constraints to access newer targeted therapies that are closely scrutinized by payers.

gMG is a case study of how the impacts on the lives of patients, families, and caregivers are underrepresented or absent from value assessments based on traditional frameworks. Definitions of value based primarily on measures like quality-adjusted life-years, mortality rates, healthcare resource utilization, and direct costs fail to account for both the everyday burden and the unmet needs that patients and their families face. This leads to undervaluing interventions and therapies that target the symptoms causing those patient-centered life impacts. To assess the true value achieved by the technologies being evaluated, decision makers must understand multiple dimensions of daily life affected by gMG and other rare diseases, and the degree of impact on caregivers, family, and society at large.

THE PATH FORWARD

To make patient-centric value assessments mainstream will require commitment to change from stakeholders across the healthcare industry.

It begins with the understanding the patients' experience of living with a rare disease. Building a strong evidence base describing the holistic burden of disease and lived experience of patients for their therapeutic areas of interest will require a collaborative effort among clinicians, researchers, patients, advocacy groups, and manufacturers.

This collaborative team should share in the development of methods to collect the data, measure, and validate these patient-centered impacts. A collective effort to refine and use validated data collection and measurement methods of patient-centered impacts— and the use of validated instruments such as the clinical outcomes assessment (COA) to measure how treatments address the indirect and non-clinical effects of rare diseases— will advance the science of patient-centric evidence. Researchers and manufacturers that design clinical trials such that the evidence generated reflects the holistic impact of the treatment on a diverse patient base will benefit from a richer understanding of their treatment's effects. Tactics to increase diversity of clinical trial participants and to select COAs and endpoints that focus on impacts that patients value will serve to further enhance that understanding.

Patient-centric models that adapt to the special circumstances of rare disease and incorporate patient-centered value elements allow value assessors and HTA bodies adhere to sound analytic methods while acknowledging the very personal impact of disease. By modifying the existing value frameworks or adopting new, patient-centric ones, value assessments will more accurately represent the full impact of health conditions and the degree to which a treatment minimizes or eliminates negative impacts.

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