Assessing the Total Economic Burden of Generalized Myasthenia Gravis

December 2023

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Funding for this research was provided by Alexion, AstraZeneca Rare Disease. Avalere retained full editorial control.

Introduction /

The Case for Considering the Total Economic Burden of Rare Diseases

Individual rare diseases (affecting 200,000 or fewer individuals) might be considered uncommon, but collectively, their widespread impact is felt by many individuals who live with or care for those with the conditions. The National Organization for Rare Disorders recognizes more than 7,000 rare diseases currently estimated to affect more than 25 million people living in the United States.[1] Additionally, more than 90% of existing rare diseases do not have treatments approved by the Food & Drug Administration (FDA), highlighting the unmet need and disease burden on patients, their caregivers, and society.[1] Rare diseases are associated with high disease severity, heterogeneity, and unpredictability; complex and burdensome treatments; and widespread societal impacts that are difficult to quantify.

Across rare and non-rare diseases, quantitative estimates of disease burden have historically relied on traditional "hard" endpoints such as clinical, cost, and utilization data, while traditional value assessments often use limited cost-effectiveness analyses from the payer perspective. This approach may underestimate the true burden of disease by focusing only on direct medical costs which constitute a fraction of the true total cost burden of the disease. Limitations of conventional health technology assessments (HTAs) are even more pronounced for rare diseases,[2] for which indirect, non-medical burdens account for more than half of the total disease burden.[3] High disease severity and unpredictability, complex and burdensome treatments, and widespread society impacts that are difficult to quantify are associated with rare diseases. Now, the industry is shifting towards a patient-centric model,[4] making it imperative to better understand the impact to patients, caregivers, and society[5] as a complement to traditional metrics, as outlined in this white paper.

Current State: What Is Known About the Burden of Rare Diseases? /

Previous Research on the Economic Burden of Rare Diseases

In 2021 the EveryLife Foundation for Rare Diseases,[6] in partnership with the Lewin Group, released the results from the National Economic Burden of Rare Disease study. This first-of-its-kind study calculated the economic burden of 379 rare diseases in an attempt to fill the existing knowledge gaps about the true overall rare disease burden. EveryLife Foundation used a mixed methods approach, leveraging claims data to estimate the direct medical costs of rare diseases and a survey to estimate the indirect and non-medical costs to patients and caregivers. Results showed that the national economic burden of rare disease totaled $966 billion in 2019, with $549 billion — over half of the costs — being attributed to indirect and non-medical costs such as work absenteeism and reduced social productivity. As the largest and most comprehensive study of the total economic burden of rare diseases to date, the study's inclusion of indirect and non-medical costing components enhanced the understanding of rare disease burden and captured costs to both patients and their caregivers that had not previously been evaluated.

While the results were a significant development for the rare disease community, a few considerations arise. First, results were reported across many groups of rare diseases, and not reported by individual rare disease. Given the unique nature of each rare disease and the resulting complex experiences of those impacted disease-specific research is a critical next step for defining disease burden for subpopulations with unique needs, challenges, and experiences. Additionally, while the research expanded upon traditional direct medical cost metrics and included indirect costs such as productivity, there are new, more patient-centered, impacts not captured by a dollar figure.

> **"I feel selfish talking about my emotional health, because I think of what she deals with**, but I do have to acknowledge that it does impact my emotional health as well. There are many nights that after I get her settled, or she's had a crises or she's had an emotional breakdown, I'll just come into my room and just cry and cry and cry, because it's exhausting."
>
> **— Caregiver participant, gMG 360**

Spotlight on gMG 360: What is Important to Patients and Caregivers?

To address a lack of existing disease-specific and patient-centered research, Avalere, Part of Avalere Health, and Alexion Pharmaceuticals collaborated on a study focused on myasthenia gravis, a rare autoimmune disease estimated to affect around 78,000 individuals in the United States.[7] Its generalized form, generalized myasthenia gravis (gMG), is characterized by weakness and disability in voluntary muscles.[8,9] This study, entitled gMG 360, used gMG as a case study to better understand the person-centered disease impact in rare disease. Using a mixed-methods approach, Gwathmey et al. first conducted in-depth interviews with patients diagnosed with gMG and their informal caregivers, who were typically family members.[7]

The gMG360 interviews led to the identification of 25 impact elements across eight domains most commonly associated with the condition (refer to **Figure 1** below). Then, the study team applied a traditional risk index model to calculate risk scores and overall weight for each impact element. Results indicate that financial and occupational impacts were among the top five life impacts related to gMG for both patient and caregiver participants. Occupational impacts are particularly significant for the population given the age of onset and disease progression, interfering with labor force participation. Study findings highlighted a need to further explore economic impacts in greater detail, with consideration for psychosocial impacts. The gMG 360 research further demonstrated that these multi-faceted, patient-centered impacts can be quantified in a way that is scientifically sound and that demonstrates the importance and degree of impact gMG has on patients and caregivers.

These seminal studies have contributed to the growing evidence base for rare disease burden. Results from gMG 360, in particular, are well-aligned with other patient-centered value frameworks. **Figure 2**, on the next page, highlights examples of traditional versus novel elements of disease burden that can be added to the patient-centered value dialogue. Future research can build upon EveryLife Foundation's survey methodology to produce a disease-specific economic burden estimate which includes the economic value of health lost to society. To the extent possible, each impact can be quantified and contextualized with qualitative impacts such as those in gMG 360 to form a novel innovative approach. For example, a larger survey sample can be used to validate the initial findings and to assess the frequency of the impact elements seen across a nationally representative sample.

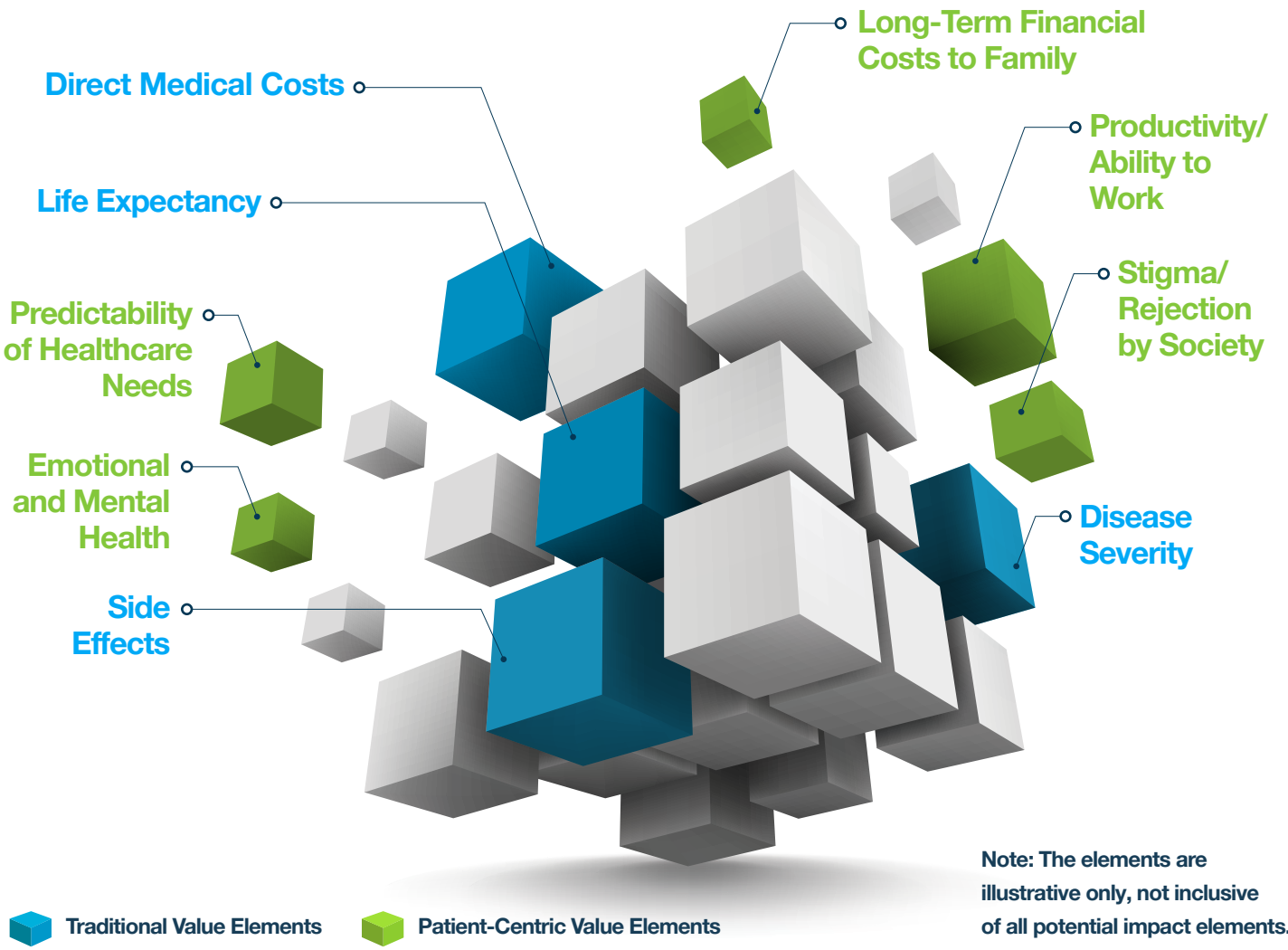
Figure 1 / gMG Patient-Centered Impact Elements

Occupational	Financial	Emotional	Physical
1. Disruptions to Occupational Advancement 2. Personal Development 3. Occupational Absenteeism	1. Reduced Personal or Household Income 2. Financial Tradeoffs 3. Financial Toxicity 4. Balance of Expenses with Quality of Life	1. Anger, Frustration, or Fear 2. Sadness and Hopelessness 3. Loss of Personal Identity 4. Potential Mistrust of Other Caregivers	1. Downstream Health Effects 2. Neglecting Healthcare Needs
Sleep	**Social**	**Planning & Autonomy**	**Safety**
1. Quantity of Sleep 2. Quality of Sleep 3. Dependence on Sleep Aid	1. Real or Perceived Social Isolation 2. Strain or Change in Relationships 3. Hobbies, Leisure, or Volunteering 4. Religious or Spiritual Attendance	1. Disruptions to Future Planning 2. Cognitive Impediments to Planning 3. Disruptions to Present Autonomy	1. Real or Perceived Physical Safety Risks 2. Real or Perceived Medical Mistreatment

"[The financial impact is] huge because, perfect example I'm on family medical leave of absence right now and I only get 60% of my pay and then I can sub with sick time, but you don't use all your sick up because you need it and then long term if I'm struggling this much now I'm only—I just turned 49—I have another 16, 17 years to work. **If I'm struggling this much now just to get to full time work if I don't make it to my retirement what is that going to look like** and I can't really save much because I have to hire so much help because I don't have the family support and it stresses me out because I have to hire in because the house has to get cleaned and there's no way I can do it... I make too much to get any kind of financial support, but I don't make enough to save and do all that at the same time."

— Patient participant, gMG 360

Figure 2 / Traditional and Novel Elements of Disease Burden



Note: The elements are illustrative only, not inclusive of all potential impact elements.

Opportunity: Real-World Applications of Total Economic Impact /

Applying Previous Learnings to Strengthen the Understanding of Rare Disease Burden

A hybrid approach, integrating techniques from gMG 360 and the EveryLife Foundation, could be leveraged in order to conduct a novel, disease-specific study, focusing on the total burden of gMG patients and caregivers. Unlike EveryLife Foundation's broader study, which assessed the economic burden of 379 rare diseases, this work could focus solely on quantifying the social and economic burden of a single rare disease, myasthenia gravis. This single disease focus would require an increased attention to detail, and rigorous study design to ensure that the unique experiences of gMG patients and caregivers were accurately captured. Additionally, by utilizing the gMG patient-centered impacts developed through gMG 360, researchers would be able to assess and validate the impacts of gMG that most affect patients and caregivers, further incorporating the patient voice into the study. Building on existing research would allow for the application and enhancement of the methods used by EveryLife Foundation to capture the out-of-pocket costs from the gMG patient and caregiver perspective as well as the productivity impacts from a societal perspective. (see **Figure 3**). In doing so, certain components of the indirect and direct costing methodology could also be altered to better fit the unique characteristics of the gMG population from leveraging a larger sample size. A novel, disease-specific study described above would better reveal some of the otherwise "invisible" burden of gMG on patients, caregivers, and society, providing relevant and actionable insights to key stakeholders.

Why Quantifying the Economic Burden of Disease is Important

To date, most value frameworks have followed a top-down approach, with priorities and endpoints driven by policymakers, payers, and other authorities. Recent models proposed by the Innovation & Value Initiative and Patient-Driven Values in Healthcare Evaluation attempt to center the conversation around the patient and caregiver perspective.[10] However, the effectiveness of these models relies on improved evidence for rare diseases, with recognition of the nuanced impacts in individual rare diseases.

The FDA's recent series on Patient-Focused Drug Development has increased the stakes—and potential benefits—for including the patient voice at multiple points of the drug development process.[11] Moreover, the guidance offers suggestions for analyzing clinical outcome assessments to identify "significantly robust" endpoints for regulatory decision-making. With this move, the FDA has set the compass in the direction of patient-focused value in drug development. However, other stakeholders are unlikely to follow unless there is a robust parallel research track focused on disease impacts (e.g., economic costs) that are not as easily measured in short- to mid-term studies of new therapies.

It is important to note that clinical trial data demonstrates the safety and efficacy of treatments and are insufficient for estimating total economic burden. Complementary research is needed to demonstrate economic value and to lay the groundwork of understanding economic impact of a disease outside of the context of a specific drug This necessitates building an evidence base to meet the needs of other key stakeholders and decision-makers to support

rare disease patients and their families. This also represents a mindset shift among drug manufacturers whose research orientation tends to focus on clinical studies of their drugs.

With these changes in national standards, it is critically important to appropriately value treatment options and inform future treatment development needs.

Economic Value of the Patient and Caregiver Perspective

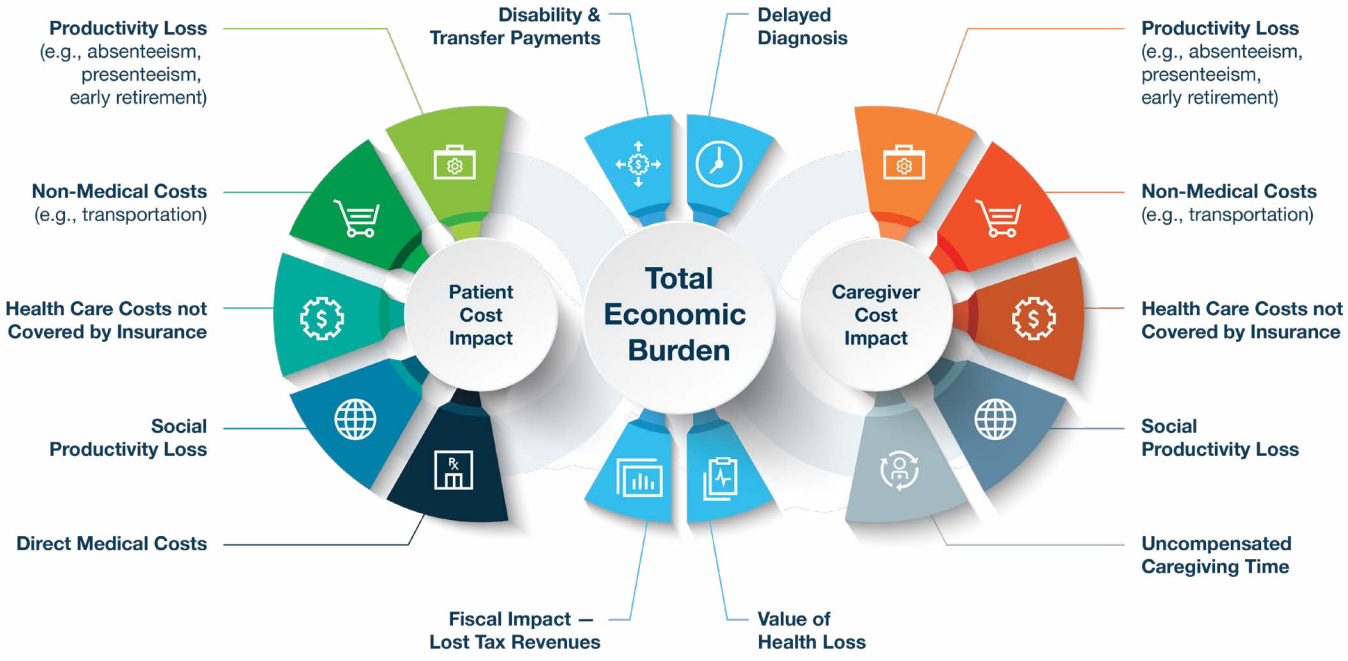
As noted by the EveryLife Foundation, the research on the economic impact of rare disease is critical to "increase the awareness of the public health crisis of rare disease, inform policy proposals, and improve the lives of patients and their families."[6] Knowledge of the true cost of these conditions, such as the significant out-of-pocket costs, as well as the impact on patient and caregiver decisions to remain productive in the labor market can lead policymakers and the public to better recognize the scale of the problem and allocate resources accordingly. Additionally, this information can help healthcare providers identify and address previously unknown or unnoticed costs and barriers to care.

Economists typically focus on dimensions of healthcare where they assume clinicians have more medical information than their patients. However, patients will often have greater understanding of the cost and burden associated with a specific disease based on their lived experience. Exploration of patient and caregiver perspectives can reduce the information asymmetry that a provider and care team may have. For example, a breakdown of life impacts by frequency and severity can reveal to providers, and the system at large, what concerns patients the most about their care and treatment, and what gets in the way of their adherence.

Implications for Stakeholders

Researchers recognize the challenges associated with calculating the total burden of disease. Nevertheless, robust and well-designed research on the total economic burden provides useful insights and context for a wide array of stakeholders.

Figure 3 / Potential Components of a Total Economic Burden Study for Rare Diseases



- **Patients** are expected to benefit from a more sympathetic and understanding system that accounts for the variety of life impacts that occur after a rare disease diagnosis. Over time, improved social support, awareness, insurance coverage, and dialogue with providers could mitigate some of the direct medical and psychological costs that impact their lives.
- **Caregivers** benefit from the recognition of their perspective. Caregiver concerns are seldom discussed and even more infrequently quantified despite the considerable ricochet impacts of a rare disease diagnosis.
- **Payers** are able to better understand, anticipate, and manage costs associated with direct medical care. Understanding indirect costs and other implications of disease burden allows for greater population management and insight into improved treatment adherence to achieve desired clinical outcomes. Offering wrap-around resources can mitigate the overall impact that newly diagnosed or existing patients experience.
- **Health Technology Assessment** bodies are cautiously optimistic about the integration of patient perspectives, but they are seeking strong rationale and compelling evidence to support its integration in final determinations. Although the family and caregiver role has yet to be formally considered by HTAs, this type of research can inform the design of future assessments.
- **Healthcare Providers** have indicated a desire to practice a "whole person approach" to care, though they may be ill-equipped with information or specific guidance on how to achieve these aims. Adopting a patient- and caregiver-centric approach for disease burden and treatments will better reflect patient needs and preferences in the accepted standards of care. With payer cooperation, the system can also reward the accepted best practices.
- **Policymakers** can formulate more effective, data-driven policies with greater likelihood of uptake by providers and payers, while also supporting outcomes deemed most important to patients and caregivers. Improved access to appropriately valued treatments may extend the labor force participation for affected individuals (patients and caregivers) contributing to increased tax revenues and reduced dependence on social benefits (e.g., early retirement or disability), among other benefits.
- **Manufacturers** are able to gain insights into the true impacts of disease which allows for development of drugs that anticipate and/or address impacts or a true assessment of current therapies to determine if impacts are addressed.
- **Researchers** can build upon the growing evidence base to inform future research and policies, learn from the methods, and implement opportunities highlighted by their peers.
- **Society** stands to benefit in multiple ways, including improved population health and "health span" and increased social productivity.

How to Contextualize Economic Estimates

Although the case for measuring and valuing the patient and caregiver perspective is well-established, implementation and operational challenges have slowed its widespread integration into national and international standards. There is no standardized definition of "value" due to different audiences, goals, and methods across existing value frameworks.[12] Patient perspectives are increasingly recognized as critical components of value, but implementation concerns prevail. For example, one of the challenges with quantifying patient and caregiver life impacts is distinguishing treatment effects from disease effects. Due to the heterogeneity of patient experiences, care must be taken when interpreting sample data and generalizing to populations. Moreover, healthcare researchers are still detangling the largescale impact that COVID-19 has had on healthcare delivery, household composition, and lifestyles.

To offset these known limitations, a well-designed approach can explore what life impacts (or elements) co-occur. To better understand patient and caregiver heterogeneity, it is critical to study the variation across subgroups and at an aggregate level. It is also important to recognize the limitations of quantitative data by complementing the research with qualitative findings based on patient- and caregiver-reported experiences.

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