

# The Hidden Burden: How Well Do We Understand the Impact of Rare Disease?



In the United States, a rare disease is defined as a single condition that affects fewer than 200,000 people.<sup>1</sup> The number of distinct rare diseases is estimated to be 7,000<sup>2,3</sup>—making the prevalence of patients with any rare disease not so rare. Recent statistics suggest that, as a whole, rare diseases affect ~25 million<sup>1</sup> people in the United States and up to 400 million people worldwide.<sup>1,2</sup> While almost 80% of rare diseases are caused by genetic abnormalities,<sup>2</sup> less than 10% (only ~500)<sup>3</sup> have a unique ICD-10 code, making diagnosis, identification, and reimbursement even more challenging for patients presenting with unique symptomology.

The Orphan Drug Act of 1983, followed by the Rare Diseases Act of 2002, are two United States federal initiatives aimed at facilitating clinical research and drug development for rare diseases. Even with these measures in place, along with advancements made over the last decade (the period with the most significant development since the Orphan Drug Act), there are still significant gaps in treatment, a shortage of medical specialists, and a dearth of disease-specific education for rare diseases. In fact, 95% of rare diseases lack FDA-approved therapies.<sup>2</sup> Moreover, after receiving diagnoses, many patients may be left without proper

therapeutic interventions because they are non-existent, restricted, or costly. However, more recently, advancements in rare disease drug development are accelerating—roughly 10% of rare diseases now have drugs in various stages of development.<sup>4</sup>

As more and more companies reach breakthroughs in treating rare diseases, it is important for the awareness of the hidden aspects of rare diseases to become more widely understood. Throughout this piece, we highlight some common themes from our research in rare disease that we find notable.

**Delayed diagnosis:** The diagnostic process for a rare disease patient can be significantly prolonged. Patients may feel isolated, misunderstood, and even helpless as they are passed from one doctor to another (with an average of 7.8 different physicians<sup>5</sup>) before finally reaching a diagnosis. Once diagnosed, there are often extended wait times for appointments with specialists and the potential need for long-distance travel once specialists have been identified. More importantly, a significant delay in diagnosis can adversely affect disease outcomes. For example, rare metabolic kidney stone disorders can be successfully managed; however, they can be overlooked for upwards of 30 years, until the patient has progressed to the point of needing dialysis. It is only at this time that the patient may discover that he or she has a rare genetic disease that could have been treated, preventing the need for dialysis.

**Silent suffering:** Due to a lag in efficient diagnosis and/or a lack of available treatments, it is not uncommon for patients with rare diseases to disproportionately suffer from non-clinical disease impacts; emotional effects can take their tolls. Lack of available clinical studies, patient education, and patient advocacy groups limit access to informed care. Patients and their caregivers are often left on their own to understand their new reality—where disease impact and progression may be poorly

understood. For instance, a patient with an ultra-rare hematologic malignancy that manifests in the skin may cycle through different medical specialists for decades without obtaining a definitive diagnosis. Without a diagnosis or support, the patient remains unaware that the disease is clinically manageable, and the emotional burden can be deleterious.

**Unconventional coping mechanisms:** Delays in diagnosis and/or lack of treatments also lead to unmet clinical needs, which can result in disease progression and inappropriate disease management. Patients may seek symptom relief from other sources, such as OTC products, herbs and supplements, alternative healthcare providers (i.e., not physicians), holistic practitioners, and any number of online remedies that tout promising results. Many of these approaches can have negative (and costly) adverse effects. With minimal support, patient behavior changes may result in “normalizing the disease” and its effects—even in the face of worsening symptoms. For example, patients with rare autoimmune peripheral neuropathies often lower their expectations in life, losing all hope of returning to a pre-disease state of functioning.

**Reduction in autonomy and caregiver burden:** Rare diseases can be chronically debilitating—even life-threatening—leading to a significant reduction in quality of life for both patients and caregivers. With decreased ability to participate in daily activities, patients may become increasingly dependent on caregivers to manage everyday needs. Moreover, research shows that patients with rare diseases experience greater social isolation, higher divorce rates, difficulty interacting at work, extended education timelines, and increasing financial burdens as they navigate their “new normal.” For instance, in rare autosomal recessive neurodegenerative lysosomal storage diseases, patients can live symptom-free for decades. When disease onset occurs suddenly, the rapid degeneration of the patient can negatively affect an entire family infrastructure, with devastating effects.

These are some of the subtleties of rare disease that require an appropriate mix of research methodologies to fully discover and interpret. Anyone interested in developing new therapies for rare disease patients should develop a research plan that provides visibility deep into these often-hidden realities. To do justice to the patient and family experience, researchers need to actively listen more than they actively ask. This can be particularly challenging because, as we have described in this piece, patients and families themselves may not fully realize, recall, or relay the details of their experiences that matter, beyond the obvious ones.

**Helping patients find their voice:** Active listening techniques help uncover behavioral patterns and hidden truths that lie deep within unique patient experiences. Some valuable techniques we can use to uncover the “lost” aspects of patient suffering include ethnographies, rare disease patient communities, and physician-patient gap analyses. The advantage of these research methodologies is that the observer gets to see things that would not normally emerge through traditional research methods (e.g., focus groups or telephone interviews).

**Ethnographies:** Ethnographies are observational studies of patients and/or caregivers in their familiar settings. The advantage of this research method is the ability to understand and naturally inquire about the context of a patient’s experience. Because patients and caregivers may have adjusted to the way they think about accommodating their “new normal,” many hidden burdens would not be uncovered in conventional research settings. Examples of hidden burdens uncovered through ethnographies include a patient with a rare genetic inborn error of metabolism, who goes through an exhausting daily ritual of specialized food preparation that requires expensive equipment and highly specialized know-how, burdening the entire household. Or the family that had to retrofit a Victorian home for handicap access, and had

to become experts in home elevator installation, spending their scarce savings, adding to the total cost of managing their child’s rare condition. Ethnographic approaches to research have benefitted from recent advances in technology, and can now be conducted effectively and compliantly by mobile apps that allow participants to chronicle their life and let researchers see, hear, and feel what it is like to live with rare diseases.

**Patient Communities:** Patient panels or communities are an excellent way to track patients longitudinally. In general, patient panels consist of engaging with patients and/or caregivers for several days/weeks/months/years and have specific metrics gathered at set intervals. This allows for a researcher to better understand the processes and experiences in rare disease patients’ lives, as opposed to a single touchpoint wherein a patient or caregiver may express something skewed from reality. In an X-linked metabolic bone disorder, for example, patients can track their worsening mobility (and accompanying burdens associated therewith, like rails or chair lifts), even when performance scores and/or other clinical metrics remain unchanged. Or, in another example, parents of children with fatal immune deficiencies can respond to validated survey instruments over time and provide robust data that can be used to build HEOR value argumentation, support publication on disease burden, or support regulatory submissions.

**Physician-Patient Gap Analyses:** It’s not uncommon for healthcare professionals to have assumptions or impressions that do not align with what is actually happening with patients or caregivers. Providing the bridge between these experiences and perceptions can vastly help in rare diseases by matching patient experience with HCPs’ perceived reality, and this can be done in blinded remote dyads or cross-matched surveys. Listening to a patient’s experience and directly matching it to a physician’s impression ultimately results in more informed patient care

by uncovering misalignments between the two participants. For example, examining stories from patients and treaters in a rare autoimmune skin condition enables the researcher to hear how patients expose themselves to additional financial and social burdens (e.g., lack of employment due to their illness) that healthcare providers may not understand or even identify. This understanding can fundamentally change the dialogue between patient and physician and can affect important decisions about treatment approach. Uncovering stories like this can also help give interested parties the tools to assist patients by closing the gaps between stakeholders.

#### References:

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Magnolia Innovation is a market research consultancy that specializes in rare and ultra-rare diseases. For more information, please visit [www.magnoliainnovation.com](http://www.magnoliainnovation.com).

