



RARE DISEASES

A Diagnostic Odyssey

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Abstract

The diagnostic journey for individuals with rare diseases often mirrors a complex detective story fraught with mystery, suspense, complications, and a resolution that remains elusive until the later stages. Patients, the protagonists of these narratives, face significant challenges initiating their journey due to the inherent obscurity of their conditions. Unlike individuals presenting with readily identifiable conditions, those with rare diseases often lack even basic starting points, such as knowing which specialist to consult given their often-complex mix of symptoms. This lack of clarity and readily available information can leave patients feeling lost and overwhelmed.

Similarly, physicians embark on a parallel investigative path, navigating a labyrinth of potential diagnoses. The process of differential diagnosis – a method of distinguishing a particular disease from others that present with similar clinical symptoms – is essential, but often unfolds as a stepwise progression, with referrals to specialists based on the emergence of new symptoms or the exclusion of previously suspected conditions, thus prolonging the initiation of appropriate treatment.

However, there are ways to overcome these challenges by leveraging innovative market research that advances understanding of rare diseases and informs treatment strategies. By uncovering and addressing inherent challenges, drug manufacturers can strive to improve the diagnostic experience, enhance treatment outcomes, and ultimately improve the lives of individuals living with rare diseases.

Introduction

In a perfect world, diagnosing and treating rare diseases would be like any given episode of the medical drama, *House M.D.*, in which the intricate and multifaceted realm of diagnosing rare diseases is vividly portrayed. The narrative follows an extraordinary diagnostician and his elite team, endowed with extensive resources, advanced diagnostic tests, and a myriad of treatment options. Their approach to differential diagnosis is exhaustive, often spanning numerous days and centered on a single patient until a definitive diagnosis is reached. This painstaking process entails several rounds of erroneous diagnoses before the climactic revelation of the correct one, typically occurring after a week or more. This idealized portrayal, however, is a glaring departure from reality.

Key Challenges in Rare Disease

A rare disease is one that affects less than 65 out of every 100,000 people worldwide, based on the World Health Organization definition [1]. In the US, a rare disease is defined as a condition that affects fewer than 200,000 people [2].

The Orphan Drug Act, passed in 1983, has changed the trajectory of rare disease drug development and approvals over the past 40 years. The development of drugs in this space has increased from 10 in the decade before 1983 – when the Orphan Drug Act passed – to roughly 20–25 per year afterwards. As of 2023, 882 orphan drugs have been FDA-approved across 392 rare diseases in the US. But with more than 7,000 identified rare diseases, much work is yet to be done [3].

While these accelerations in drug development represent progress and provide hope, patient identification and diagnosis remain major hurdles. Unlike in *House M.D.*, the reality faced by most patients with rare diseases is a stark contrast. The majority do not have the advantage of being under the care of such exceptional medical professionals, in a highly specialized hospital, as portrayed in the television series. If we were to remove the extraordinary diagnostician and the dedicated team from the equation and instead incorporate multiple patients, several medical facilities and practitioners,

along with the hurdles associated with access to care, we would approach a more accurate depiction of the real-world experience of patients with rare diseases. Frequently, these patients endure a protracted diagnostic journey spanning several years and involving numerous consultations with a variety of doctors in different locations before receiving an accurate diagnosis; tragically, some never do.

In addition, the prognosis in real life differs starkly from that in an episode of *House M.D.*, in which patients are often portrayed as recovering miraculously following the correct diagnosis despite being on the brink of death merely hours or days prior. The reality is far less optimistic. Historically, there were limited treatment options available, with most strategies focusing on disease management rather than cure. Although not all rare diseases pose a direct threat to life, many are chronic in nature, necessitating long-term management or treatment. Patients are frequently faced with unexpected flare-ups, attacks, relapses, or are refractory to multiple lines of treatment and experience progression of disease, which significantly impacts their health and quality of life. Consequently, adjustments to daily life are often required to accommodate the ongoing presence of the disease.



A pervasive lack of knowledge and confidence regarding rare diseases among healthcare professionals often leads to multiple misdiagnoses and protracted diagnostic odysseys.



The rare disease landscape presents a multifaceted array of challenges, impacting patients, physicians, and researchers alike. These challenges encompass a spectrum of issues, including:



Knowledge Gaps and Diagnostic Uncertainty

A pervasive lack of knowledge and confidence regarding rare diseases among healthcare professionals often leads to multiple misdiagnoses and protracted diagnostic odysseys. The intricate nature of these conditions, coupled with limited familiarity with confirmatory testing methods, further complicates the diagnostic process.



Intricate Disease Pathways and Symptom Management

The complex and often poorly understood pathways of rare diseases, along with the diverse range of symptoms they manifest, pose significant challenges for effective treatment. This complexity underscores the critical importance of disease state education and market-shaping initiatives to enhance physician understanding and facilitate timely referrals to appropriate specialists.



The Detrimental Impact of Misdiagnosis and Delayed Diagnosis

Misdiagnosis represents a critical factor in the rare disease journey, with patients frequently receiving inaccurate diagnoses before ultimately being referred to specialized centers. The National Organization for Rare Disease reports that it can take 5 years or more for a person with a rare disease to receive the correct diagnosis [4]. This delay in accurate diagnosis can significantly impact a patient's quality of life, delaying the initiation of appropriate treatment and potentially rendering potential therapies ineffective.

Addressing the Challenges

Several factors warrant consideration when mitigating these challenges. Enhanced disease state education initiatives aimed at increasing physician awareness of rare diseases, their symptomatology, and available diagnostic tools are crucial. Facilitating efficient referral pathways to ensure patients are directed to the appropriate specialists in a timely manner is also paramount. Patient advocacy groups play a critical role in the rare disease community by providing support, education, services, and a sense of community for patients and caregivers. They also offer pharmaceutical and biotech companies a way to connect with the community and gain empathy and insights into their experiences.

The Role of Market Research

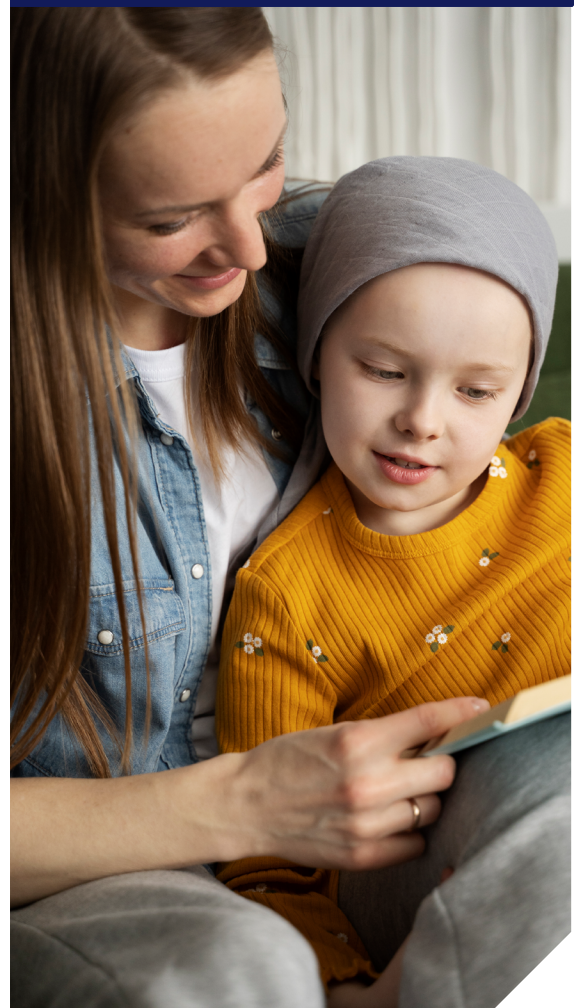
Market research is one of the solutions companies can utilize to mitigate the challenges inherent to rare diseases. It allows connection with physicians who may see these patients during their journey to diagnosis and treatment, the patients and caregivers themselves, and other stakeholders. Research helps gauge these groups' knowledge, beliefs and perceptions and provides guidance on how to engage with them accordingly.

Developing innovative and robust methodologies for conducting market research in rare disease populations advances understanding and informs treatment strategies. By addressing these challenges, we can strive to improve the diagnostic experience, enhance treatment outcomes, and ultimately improve the lives of individuals living with rare diseases.

Given the small size of these populations of patients and doctors, conducting research can also feel like an odyssey throughout the recruit, design, and execution stages. Specialist expertise in rare disease research is therefore critical.



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Challenges Across Market Research Study Components

Recruitment



Identifying patients is a challenge in terms of market research processes, similar to the challenge pharmaceutical companies face in helping physicians identify patients for their treatments. A successful recruit for the rarest of conditions often entails a combination of outreach efforts that may include working with patient advocacy groups, networking on social media, running ads, and HCP referrals, among other approaches.

Design



Instrument design must prioritize capturing maximum insight within a limited timeframe. Given recruitment challenges for patients and practitioners, studies must maximize data acquisition without overburdening participants through excessively lengthy surveys or discussions.

Impact



Research in rare diseases necessitates agility and adaptability, demanding a readiness to adjust strategies, refine hypotheses, and thoroughly explore unexpected avenues to uncover even the smallest pieces of information, all within the constraints of limited sample sizes.

Chart audits are one important tool in rare disease research, given that large patient samples are unavailable. They provide a comprehensive view of the patient journey, from diagnosis and treatment to current health status, by analyzing real patient charts via healthcare providers. This method offers in-depth insights into physician practices and treatment patterns for specific rare diseases, going beyond typical treatment approaches. In addition, in many rare diseases, there is no typical patient. The granularity of data obtained from chart audits allows for a thorough understanding of the disease and can reveal unique insights valuable for drug development and research.

Ultimately, effective market research in the rare disease space requires an approach that mirrors the complexities of diagnosis and treatment. It must be flexible enough to adapt to the evolving understanding of a disease, accommodate the challenges of limited patient populations, and delve into the intricate nuances of each individual medical journey. Just as a thorough exploration of possibilities is essential in differential diagnosis, market research must be prepared to navigate a similarly intricate path to uncover insights that shine a light on patients' needs and steer the development of impactful solutions.



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