

Rare and orphan diseases: Challenges and opportunities



Safiya Bee*, Priyanka Soni

Mandsaur University, Mandsaur, Madhya Pradesh

Email: safiyaanees94@gmail.com

Abstract

Rare and orphan diseases, also known as rare disorders, encompass a diverse array of prerequisites which collectively impact a substantial number of people worldwide. Despite their low individual prevalence, these diseases pose multifaceted challenges for patients, health stakeholders, and pharmaceutical companies. This comprehensive review article delves into the intricate landscape of rare and orphan diseases, exploring their definition, epidemiology, diagnostic complexities, treatment options, and the ongoing efforts to change the unique hurdles associated with these conditions. By shedding light on this often-overlooked area of healthcare, we aim to bring the issue to light and encourage widespread understanding, and ultimately pave the way for improved outcomes and quality of life for those affected by these rare disorders.

Keywords: Rare diseases, Orphan diseases, Diagnosis, Precision medicine, Orphan drugs

1. Introduction

Rare and orphan diseases are a heterogeneous group of conditions characterized by their low prevalence, typically affecting fewer than 200,000 individuals in the United States or fewer than 1 in 2,000 individuals in the European Union (EU). These disorders can be inherited or acquired, affecting individuals across all ages, genders, and ethnic backgrounds. The term "orphan" is derived from the historical lack of commercial interest from pharmaceutical companies in developing treatments for these conditions due to the small patient population and the perceived low return on investment. However, recent advancements and policy changes have catalyzed a shift in this landscape, with increasing recognition of the urgent need to address the unmet medical needs of those affected by rare diseases.

2. Epidemiology and classification

Depending on different sources, the number ranges from 6,000 and 8,000 distinct rare diseases identified worldwide, collectively affecting millions of people globally. Accurately measuring the prevalence of these conditions is often a hurdle to determine due to the lack of comprehensive, centralized registries and the inherent challenges associated with diagnosis. Rare diseases can be classified based on their underlying etiology, affected organ systems, or specific characteristics, encompassing a wide range of disorders, including genetic or metabolic disorders, rare cancers, autoimmune diseases, and rare infectious diseases (1-3).

3. Diagnosis and challenges

The journey to an accurate diagnosis for individuals with rare diseases is often arduous and fraught with numerous obstacles. Many patients experience a protracted diagnostic odyssey,

enduring multiple misdiagnoses, referrals, and extensive testing before finally receiving an accurate diagnosis. This diagnostic delay may have significant consequences for disease management, treatment outcomes, and the overall well-being of patients and their families. Furthermore, the lack of awareness and specialized knowledge among healthcare professionals regarding these rare conditions can exacerbate the diagnostic challenges, leading to further delays and misdiagnoses.

Table 1. This table provides relevant statistics and information on the epidemiology, diagnosis, treatment, regulatory frameworks, patient advocacy, and funding aspects related to rare and orphan diseases.

Parameter	Statistics/Information
Estimated number of rare diseases worldwide	6,000 - 8,000
Collective population affected	Millions of individuals
Prevalence threshold for diseases in the US	Affecting fewer than 200,000 individuals
Prevalence threshold for diseases in the EU	Affecting fewer than 1 in 2,000 individuals
Percentage genetic etiology	Approximately 80%
Percentage affecting children	Estimated 50%
Average time to receive an accurate diagnosis	5--7 years (in some cases, up to 30 years)
Number of approved drugs in the US (as of 2022)	Over 600
Number of approved drugs in the EU (as of 2022)	Around 200
Estimated cost of developing	\$500 million - \$1 billion
Average annual cost	\$150,000 - \$500,000
Percentage with no approved treatment	Approximately 95%
Percentage with no approved treatment	Over 7,000
Estimated annual funding research in the US	\$3.7 billion (NIH, 2022)
Estimated annual funding in the EU	€1.5 billion (Horizon Europe, 2021-2027)

4. Treatment and therapeutic development

Treatment availability for rare diseases are frequently limited or non-existent, leaving patients and their families grappling with significant unmet medical needs. For some conditions, supportive care and symptom management may be the only available approach, while later may have an upper hand from off-label use of existing therapies. However, in recent years, advances in fields such as genomics, molecular biology, and personalized medicine have paved the way for the development of targeted therapies tailored specifically for rare diseases (4). These innovative approaches include gene therapy, enzyme replacement therapy, and small molecule drugs designed to target the underlying molecular mechanisms of these conditions. Despite these promising advancements, the substantial financial burden of research and development combined with the small patient population, can make it challenging for pharmaceutical companies to justify the substantial investment required to bring these therapies to market (5).

5. Regulatory frameworks and incentives

Recognizing the unique challenges associated with rare and orphan diseases, various regulatory frameworks and incentives have been established to encourage and facilitate research and development in this field. In the United States, the Orphan Drug Act of 1983 was a pioneering legislative effort that provided financial incentives, such as tax credits, market exclusivity, and fee waivers, for pharmaceutical companies engaged in developing treatments for rare diseases. Similarly, the European Union established the Orphan Medicinal Products Regulation, offering comparable incentives to promote research and development efforts focused on addressing the unmet medical needs of patients with rare disorders.

6. Patient advocacy and support

Patient advocacy organizations play a pivotal role in the rare disease ecosystem, serving as a powerful voice for those affected by these conditions. These organizations tirelessly raise awareness, provide invaluable support, and advocate for the rights and needs of individuals living with rare diseases and their families. They often serve as a vital bridge, facilitating collaboration and communication among patients, healthcare providers, researchers, and policymakers, driving progress in research, diagnosis, and treatment. Additionally, patient advocacy groups offer a range of educational resources, support groups, and practical assistance in navigating the complexities of the healthcare system, ensuring that no patient or family member faces these challenges alone (6).

7. Challenges and future directions

Despite the significant strides made in recent years, numerous challenges persist in the field of rare and orphan diseases, impeding progress and limiting access to effective treatments and supportive care. One of the most pressing challenges is the lack of comprehensive, global registries and data repositories, which hinders our ability to accurately track and study these conditions. Additionally, limited funding for research and the urgency of fostering collaboration among key players pose significant barriers to advancing our understanding and developing novel therapies (7,8).

Moreover, even when approved treatments become available, access can be limited, particularly in resource-constrained settings or regions with inadequate healthcare infrastructure. Addressing these multifaceted challenges requires a concerted and collective action in healthcare. To drive progress and improve outcomes for those affected by rare diseases, several initiatives and strategies have been proposed:

- 7.1** Establishing robust international collaborations and data-sharing platforms to facilitate research efforts, enhance our understanding of these rare conditions, and accelerate the development of effective treatments.
- 7.2** Promoting public-private partnerships and exploring innovative funding models to support and incentivize research and development initiatives targeting rare diseases.
- 7.3** Enhancing awareness and education among healthcare professionals to improve diagnosis, management, and access to available treatments and supportive care services.

- 7.4** Advocating for policies and healthcare reforms that prioritize equitable access to approved treatments, supportive care, and comprehensive services for patients with rare diseases, regardless of their geographic location or socioeconomic status.
- 7.5** Encouraging active patient involvement and engagement throughout the research and development process, ensuring that patient perspectives, needs, and priorities are at the forefront of these efforts (9,10).

8. Conclusion

The landscape of such diseases is complex, multifaceted, and presents a different area that require a coordinated and multidisciplinary approach. Despite the significant strides made in recent years, driven by scientific advancements, policy reforms, and the tireless efforts of patient advocacy groups, the journey towards achieving comprehensive and equitable care for those affected by these conditions is far from over.

As we look towards the future, several key priorities emerge as critical to driving meaningful progress and maintaining consequences for patients with rare diseases:

- 8.1** Establishing robust, global collaborative networks and data-sharing platforms: By fostering international collaborations and centralizing data repositories, we can accelerate research efforts, enhance our motive of the mechanisms and natural history of these conditions, and expedite the development of effective diagnostic tools and targeted therapies.
- 8.2** Sustainable funding and innovative financing models: Addressing the significant financial barriers that hinder research and development initiatives requires a concerted effort to secure sustainable funding sources and explore innovative financing models. Public-private partnerships, venture philanthropy, and outcome-based payment models could provide high knowledge for supporting rare disease research and ensuring access to approved treatments.
- 8.3** Strengthening healthcare infrastructure and capacity building: In many regions, limited healthcare resources, inadequate infrastructure, and a lack of specialized expertise pose significant barriers to timely diagnosis, proper management, and access to available ailments of such diseases. Investing in capacity building, education, and training for professionals in healthcare sector, as well as strengthening healthcare systems, is crucial to ensuring equitable access to comprehensive care.
- 8.4** Patient-centered approaches and engagement: Placing patients at the center of rare disease research, policy development, and healthcare delivery is essential for ensuring that their needs, priorities, and perspectives are adequately addressed. Encouraging active patient engagement throughout the research and development process, as well as in the design and implementation of supportive care services, can lead to more meaningful and impactful outcomes.
- 8.5** Regulatory harmonization and policy reforms: While regulatory frameworks and incentives have been instrumental in driving rare disease research, there is a need for greater harmonization and coordination among different regions and countries. Streamlining regulatory processes, aligning incentives, and implementing policies that prioritize access to approved treatments and supportive care services can help overcome geographic disparities and ensure that no patient is left behind.

Addressing the multifaceted challenges associated with rare and orphan diseases requires a concerted, global effort that transcends borders and disciplines. By fostering collaboration among patients, researchers, pharmaceutical companies, policymakers, and other stakeholders, we can collectively work towards a future where no disease remains truly orphaned, and where those affected by these conditions have access to timely diagnosis, effective treatments, and comprehensive supportive care services, ultimately improving their quality of life and reducing the immense burden imposed by these rare disorders.

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