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Rare Diseases and their Unique Challenges

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ABSTRACT

By definition, rare diseases affect a very small percentage of the population; however, that fraction still represents a significant 300 million people worldwide. The scarcity of affected patients and knowledgeable clinicians for each rare disease presents multiple unique challenges for all individuals and institutions involved. Clinicians struggle because the rarity of these diseases prohibits easy access to information about symptoms, which leads to delays in accurate diagnosis. Patients struggle with the uncertainty of living with undiagnosed conditions, which can lead to lowered quality of life and an economic burden, as well as anxiety issues and depression. Additionally, researchers and pharmaceutical companies have difficulty finding adequate patients for clinical trials, while dealing with uncertain commercial viability of any treatment. This coupled with the myriad of rare diseases means there is not enough funding for each disease to make significant progress in short amounts of time. The lack of recognition from governments and international organizations until recently slowed any progress made towards rare disease treatment. Solutions to these challenges will require a multi-pronged approach consisting of digital platforms such as patient networks, increased training among physicians, new treatment strategies like precision medicine, government intervention, as well as incentives for companies to invest in rare disease treatment. The key to eventually solving each challenge is awareness of the public and medical community alike.

Introduction

A person suddenly falls very ill. Every doctor they consult proclaims a different diagnosis and prescribes a different treatment regimen. The symptoms of the illness persist, and it affects their physical and mental well-being. They become financially insecure because of the enormous amount of money going into the treatments, and at the same time, their professional and social life suffer because of the illness. The lack of diagnosis also affects their insurance coverage. This is the story of many individuals affected by rare diseases.

The criteria for what makes a disease rare varies as per different international standards. For example, there are 196 definitions from 1109 organizations of what a rare disease (RD) is (Amalanathan, 2023). The European Union defines a rare disease as affecting less than 1 in 2000 individuals (Taruscio and Gahl, 2024), while the Orphan Drug Act of 1983 designates a disease as rare in the USA if it affects less than 200,000 people in the country (Ferreira, 2019). Although they are labeled “rare”, there are more than 300 million people globally living with various rare diseases. There are about 7000 known rare diseases, (Rare diseases, common challenges, 2022) of which only 5% are treatable (Ferriera, 2019).

The nature of specific rare diseases varies drastically, and the incidence rate for each disease varies as well. A more common example is Hemophilia, caused by a change or deficiency in blood clotting factors. This causes a patient's blood to not clot following an injury and can lead to painful joint bleeds even after minor trauma. It can be problematic because lack of treatment can cause extreme bleeding even from minor injuries, as well as frequent internal bleeding (Blog) and crippling joint bleeds. According to the CDC, an estimated 33,000 men live with hemophilia in the USA (Centers for Disease Control and Prevention, 2024). A far more rare disease known as Fibrodysplasia Ossificans Progressiva (FOP), is a musculoskeletal condition where muscles and tendons are slowly transformed into

bone, causing the patient to have a "second skeleton." Globally, it is estimated that FOP affects about 1.36 per million people, and it differs by country and region. (Al Mukaddam et al., 2022). An FDA-approved treatment for FOP was only released in August of 2023 (Talha and Ali, 2024).

Rare diseases are particularly difficult to diagnose and treat due to their varied presentations and a lack of information and funding for each disease. In 1989 the US National Commission on Orphan Diseases highlighted the problems encountered by patients with RD, including delays in diagnosis, challenges in obtaining medical treatment, and inadequate training of healthcare workers to diagnose rare diseases. In 2016-2017, an ENSERio study that explored patients' experiences and expectations concerning access to diagnosis, treatment, healthcare, and social services proved that these problems still exist (Gimenez-Lozano et al., 2022). As a result, individuals with these diseases and their families encounter greater risks of facing poor quality of life, heightened mental health challenges, increased social isolation, and worse work-life balance (Adachi et al., 2023). This is compounded by a lack of knowledge about rare diseases even among physicians, causing difficulty and delays in diagnosis, as well as hesitancy for big companies to invest in cures, which slows down research as a whole (Kremer, 2004). This paper reviews prior literature on rare diseases to analyze the challenges regarding rare diseases from the perspective of multiple stakeholders such as physicians, patients, the pharmaceutical industry, and the government. It concludes by proposing various solutions on how these challenges can be addressed.

Rare Disease Challenges

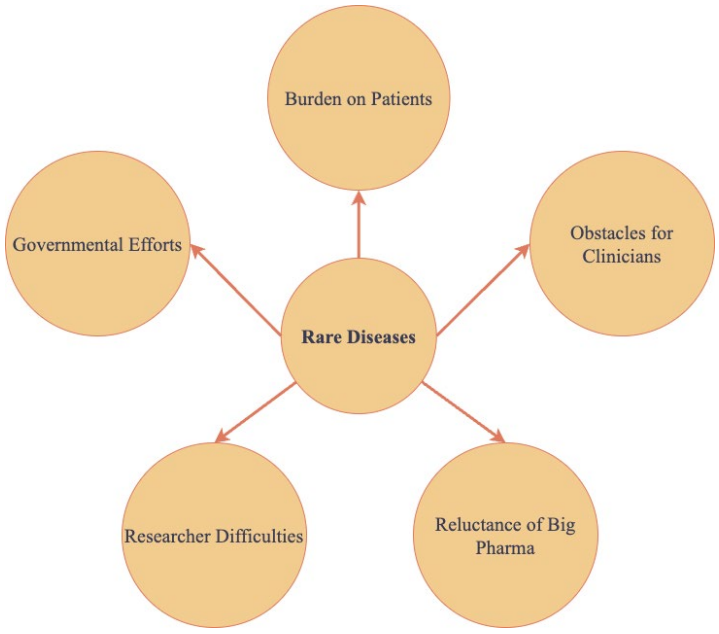

Figure 1. Main challenges brought forth by rare diseases

Obstacles for Clinicians

Knowledge Gap

One aspect that makes RD's particularly difficult to treat is the general lack of knowledge and resources surrounding them. Clinicians often have difficulty caring for patients with diseases they haven't seen before, as a clinician's chances of correctly diagnosing a disease directly correlates to the number of patients they see with that disease

(Stoller, 2018). For rare diseases that are sparsely encountered, the first hurdle for clinicians is to understand the direction in which to pursue testing to find a diagnosis. Only then can they try to refer to specialists who may have knowledge in that field or may attempt a misinformed diagnosis. Patients struggle to find physicians who possess expertise about their rare condition, and because of this many go undiagnosed.

Delay in Diagnosis

In Europe, 1 in 4 patients with RD have a delay in diagnosis of about 5 - 30 years from the start of disease symptoms, and 2 in 5 patients have received several misdiagnoses (Gainotti, 2018). A lack of universal guidelines to help diagnose these diseases only exacerbates the clinician's difficulties. These difficulties were demonstrated in the Spanish rare disease registry, which analyzed 3,304 members, and showed that more than 20% of individuals waited more than 10 years for a diagnosis (Taruscio and Gahl, 2024). Other studies show that people living with rare diseases typically wait an average of five years to receive an accurate diagnosis, which exacerbates the psychological burden of their condition (Delaye et al., 2022). These extensive waiting periods are problematic for patients as their conditions can get worse, and a lack of diagnosis causes issues with insurance coverage. Not only does it take time, but many patients have to meet several specialists and healthcare providers before being diagnosed. Still, these diagnoses can be wrong, preventing them from getting the treatment and care that they need (Garrino et al., 2015).

Burden on Patients

Quality of Life

RD’s leave a tremendous burden on those affected, encompassing not only economic and healthcare-related, but also causing a dramatic loss in quality of life. A study based in Spain found that the most common effect of RDs was interference in daily routine caused mostly by the disease itself as well as delay in diagnosis (Gimenez-Lozano et al., 2022). RDs are found to result in significant pain and greatly impact the mental health and overall well-being of a person affected. Patients often report anxiety and depression in addition to condition-specific symptoms (Uhlenbusch et al., 2019). These additional health detriments are an unaccounted cost of having rare diseases that affect every aspect of a patient’s life.

As the disease takes hold of the patient and their likelihood of experiencing mental health issues continues to rise, social isolation and discrimination caused by rare disease related health conditions follow closely (Adachi et al., 2023). This leaves the patient and their caregivers with a much poorer health-related quality of life (HRQoL) compared to the average population. 2079 RD patients pooled a utility score of 0.57 and the mean utility score (MUS) of their caregivers was 0.78, much inferior to the average population with a MUS of 0.92 (Chung et al., 2022). These intangible effects on the lives of patients and those closest to them are what make the challenges of rare diseases so distinct from other disorders.

Financial Hardships

RD’s often leave patients extremely dependent, to the point where family members or friends are forced to act as informal caregivers. These caregivers coordinate care and help with the patient’s daily activities, causing large hindrances in their own personal lives and careers. Because of this, many patients opt to hire paid carers, forcing the patient and their financial supporters to stay in the workforce longer (Chung et al., 2022). Expensive and sparse treatments leave these financial supporters devastated, with an Australian study finding 45% of parents of affected children unable to afford their children's medical costs, with 29% having to work more hours or take a second job (NSAA,

2017). A study from China found that 90% of patients could no longer afford their living expenses (Adachi et al., 2023).

Reluctance of Big Pharma

Due to the nature of rare diseases, those affected are few and far between, making it extremely difficult for researchers to conduct clinical studies on large populations (Stoller, 2018). Lack of funding is a critical problem facing rare diseases research. This is counterintuitive, however, considering that in the 2023 fiscal year, the National Institute of Health (NIH) allocated $6.9 billion towards rare diseases (Mikulic, 2024). However, when that money is divided among the 7,000 known diseases, it amounts to less than a million dollars per disease. This causes a dilemma where there is apparently a lot of money for 'rare disease' funding, but each individual disease isn't receiving enough to discover meaningful treatment. In 2014, the Office for Rare Disease Research estimated that around 10 percent of NIH research funding, roughly $5 billion, is allocated to rare disease research, but only about $12 million of this amount is specifically directed toward clinical research (Strandburg et al., 2014). This lack of funding for specific diseases is because major federal funding agencies like to invest more in research on common diseases since the societal impact of such investments is higher. Additionally, large pharma companies are reluctant to invest because it takes much longer for these corporations to obtain a return on their investment as compared to common diseases such as asthma, and diabetes (Graf von der Schulenburg and Frank, 2015). Rare disease research has a much longer payback period because of the small market size. Another factor is the nature of RDs. Since the population of rare disease patients is so small, companies are likely to set high prices for drugs to achieve profitability. In contrast, since common diseases affect a larger number of people, a more affordable pricing strategy can be effective for everyone (Kremer, 2004).

Currently, there are only a few therapies that have been studied and approved for rare diseases, and a few more that exist but are far too expensive for most affected individuals. The free market is unable to solve the problem of expensive therapies because of steep costs of creating drugs and extreme prices of current therapies that prevent people from buying them (Pingali and Das, 2021). This comes from the fact that it costs over $2 billion to get one drug into the market (DiMasi et al., 2016). Because of the inability of the market to fix itself, governments have to intervene.

Governmental Efforts

In the USA

With so many people affected all over the world, governments everywhere are getting involved to fund research and incentivize drug production for RDs. In 1983, the US government authorized the Orphan Drug Act (ODA) to motivate pharmaceutical companies to manufacture drugs for RDs by providing market exclusivity and tax incentives (Roberts and Wadhwa, 2023). Before its passage, there were only about two RD drugs/year being approved by the United States Food and Drug Administration (FDA). Now, over forty years later, scores of "orphan" drugs have received approval. According to Fermaglich et al, "to receive orphan drug designation, sponsors must submit a request to the FDA's Office of Orphan Products Development (OOPD) and meet two principal designation criteria." The first criterion is to show that the drug is intended for treatment, prevention, or diagnosis of a rare disease. The second criterion is to present data that provides a scientific justification for the medicine's potential effectiveness (Fermaglich and Miller, 2023). Over time, both orphan drug designations and approvals have risen remarkably. In the last decade, there have been almost 7-fold more designations in comparison to the first ten years after the ODA was enacted. Likewise, there has been a 6-fold increase in initial approvals during the same decade. In 2002, the US government also passed the Rare Disease Act, which established the Office for Rare Diseases Research (ORDR) to handle rare disease research

(Shimkus, 2002). However, even with all these drug designations and diseases, there are still no drugs available for a large majority of rare diseases, with only about 1000 diseases represented by the 6340 orphan drug designations (Fermaglich and Miller, 2023).

Rest of the World

RDs have only recently caught the attention of the international community and officially been recognized as a matter of concern by leading international organizations (Adachi et al., 2023). In May 2019, rare diseases were included on the World Health Organization Assembly's agenda for the first time. At the event, case studies of rare diseases were utilized to demonstrate how life-changing digital technologies can help achieve the goal of universal health coverage, which is leaving no one behind. Another example of worldwide recognition is a UN resolution passed in 2019. Due to the shared goals between rare disease endeavors and universal health coverage, the UN emphasized the significance of acknowledging rare diseases in health policies. Rare Disease International, the European Organisation for Rare Diseases (EURORDIS), as well as the Committee on Non-Governmental Organizations (NGOs) for Rare Diseases jointly urged the UN for a resolution to recognize the demands and obstacles of rare disease patients and their caregivers (Chung et al., 2022). This resolution aimed to enhance the inclusion of rare diseases into the agenda of the UN and advance its commitment to realizing the Sustainable Development Goals (SDGs) (Adachi et al., 2023).

Addressing Rare Disease Challenges

Since the challenges posed by rare diseases are multi-dimensional, the solutions to address these should be equally comprehensive. Rare diseases present unique hurdles to stakeholders such as patients, doctors, governments, and big pharma, and there are avenues for each group to get more involved and aid in diminishing the burden of RDs.

To address the financial burden and poor quality of life caused by RDs, patient advocacy groups that can bring together patient communities are highly effective (Stoller, 2018). Organizations can focus on advocacy and raising awareness for the disease, but also build a network of patients to communicate and relate to each other in order to lessen the burden of their medical condition. Patient portals such as patientslikeme.com are also useful resources where people can connect with others having similar conditions, and exchange treatment and lifestyle information. Also, The New York Times runs a monthly column titled "Diagnosis" where patient symptoms are presented, and draws readers in to offer potential diagnoses for these patients.

Patients suffering from rare diseases can also be alleviated by shortening the long process of diagnosis. These delays in diagnosis are largely caused by a lack of expertise and education on rare diseases, and can be mitigated by providing more training and collaboration to clinicians at every care level. As awareness grows about the challenges of rare diseases and the importance of finding solutions, international collaboration among doctors has become essential to tackle these issues and develop treatments(Schieppati et al., 2008). Additionally, a study by the National Organization for Rare Disorders (NORD) revealed that nearly half of rare disease patients and caregivers found a lack of clinical specialization as a significant hindrance causing delays in diagnosis (NORD, 2020). As evidenced by a rare disease population in Valencia, Spain, the training of professionals in rare diseases must encompass not only clinical aspects but also socio-health aspects. This approach will enable clinicians to fully utilize all available resources (Gimenez-Lozano et al., 2022).

95% of rare diseases don't have approved treatment (Health, 2024). Because of this, patients have to receive some form of non-specific treatment to alleviate their symptoms. These patients require definitive diagnosis through precision medicine which will help them get personalized treatment. This will enhance the chances of treatment success while reducing the risk of drug toxicity for each individual patient by customizing treatment to align with the unique characteristics of each patient (Villalón-García et al., 2020). The interesting thing about precision medicine is

that it works better for rare diseases than most common diseases. This is because most rare diseases, about 80%, are inherited through genetic alterations (Health, 2024).

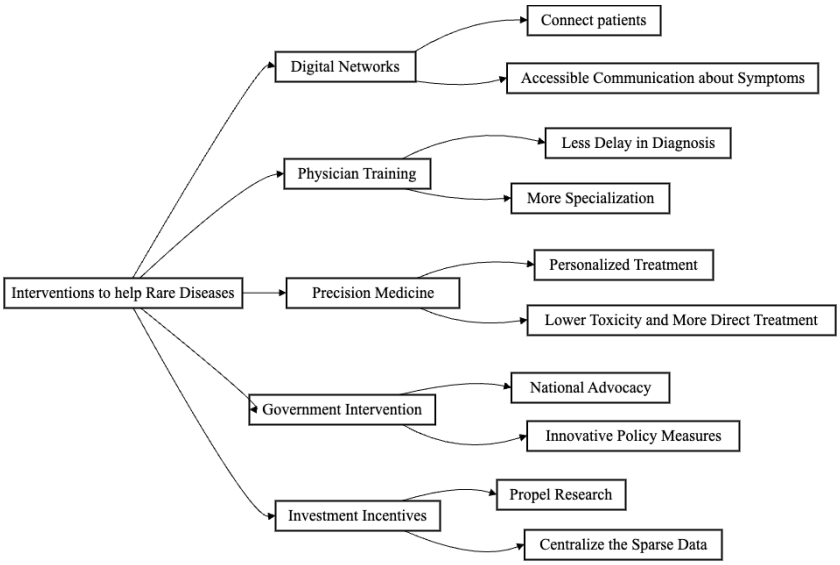

Figure 2. Multipronged approach to address rare disease challenges

As demonstrated by the US government, WHO, and the UN, implementing policies to prioritize RDs allows for significant progress in acquiring funding, furthering research, and especially raising awareness. By passing acts such as the Orphan Drug Act, the US was able to dramatically increase the number of drugs produced annually for rare diseases. The UN passed a resolution to acknowledge the needs and challenges faced by rare disease patients and their families. This led to them also emphasizing the need for recognizing rare diseases in policy. Governments can have a pivotal part in increasing awareness of RDs by assigning fixed budgets, collaborating with drug manufacturers, and generating additional funds through creative policy measures (Pingali and Das, 2021).

In the long run, government funding can only carry research so far. For typical diseases, big pharma companies are a large portion of funding for research and treatment. However, they often stray away from rare diseases because of the lack of direct impact on patients, caused by the small patient population and knowledge gap about the diseases. To address these issues, large pharmaceutical companies should receive additional incentives to spend money on research and development of drugs for rare diseases. These companies could also significantly contribute by collecting information to support the formulation of research policies and by enhancing the monitoring and centralization of data (Adachi et al., 2023). Additionally, having a more "efficient, equitable, and sustainable" approach to rare disease research ensures that RD patients can take advantage of every resource available to them (Halley et al., 2022).

A pivotal way to improve care of rare diseases is 'not just the funds, it's the awareness,' as stated by Audrey Gordon, president and executive director of the Progeria Research Foundation, a non-profit organization that promotes the study of progeria, a rare disease (Dance, 2011). The lack of awareness is the most significant problem facing those affected by RDs. Ultimately, the most effective way to resolve the issues of rare diseases is to educate both professionals as well as the general population about the unique challenges caused by them. Education facilitates a push for policy change, more funding, and more knowledge for patients and clinicians alike. RD education in universities and medical schools will inspire bright minds to enter the field, hopefully implementing these strategies to better the lives of people affected by rare diseases. Ultimately, the ability to make change lies in the hands of ordinary people touched by rare diseases; through collective efforts to raise funds and awareness, they can create a profound and lasting impact.

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