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# Rare Diseases: Biomarkers Associated and Challenges with Public Health

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## Abstract

Rare diseases, often referred to as orphan diseases, include a heterogeneous group of disorders that affect a limited number of individuals within the population. Despite their rarity, the cumulative impact of rare diseases is significant, as they collectively affect millions worldwide. Biomarkers have emerged as crucial tools in the identification, diagnosis, and monitoring of rare diseases. However, the study and management of rare diseases pose unique challenges for global public health and healthcare systems. Limited understanding of the underlying mechanisms, scarcity of patient data, and lack of available treatments contribute to diagnostic delays and treatment uncertainties. Global collaboration is imperative to address these challenges and improve the outlook for individuals affected by rare diseases. This abstract discusses the importance of biomarkers in rare disease research and clinical practice, highlighting their potential to transform diagnosis and treatment paradigms. It highlights challenges faced by global public health systems, such as limited awareness, diagnostic delays, and limited access to effective therapies. It also highlights future trends in rare disease management, emphasizing multidisciplinary collaboration and technological advancements to improve lives affected by these conditions. As we navigate the complexities of rare diseases, a concerted effort from researchers, clinicians, policymakers, and advocacy groups is essential to drive progress and pave the way for a more equitable and effective rare disease healthcare landscape.

**Keywords:** Rare diseases; Global public health; Biomarkers; Health care services; Genetics

## Introduction

Rare disease is usually uncommon and describes a condition that only affects a minor portion of the population. The exact reason or cause for these rare diseases are still unsolved, still the portion of the disease is being traced according to affected mutant in a single gene. Many rare diseases appear in young stage of life and many die before they turn 5 years of age. Patients with rare diseases confront particular difficulties in being diagnosed and receiving medical care, and support services [1].

As a result of the genomics revolution over the past three decades, research on rare diseases has advanced dramatically. This has significantly altered the global policy environment, and shared challenges and insufficient medical and social requirements have yet to be seen [2]. There are various contrasting statistics on rare diseases in medical publications and on the Internet, including the specific the total number of rare conditions, their cumulative prevalence, and the percentage of rare diseases with a genetic cause. However, in many instances, the specific quantity is either not agreed upon or the claimed numbers are not validated by the scientific literature [3]. There are 6,000-8,000 distinct rare disease diagnosed, with 50%-75% having childhood onset and 80% possessing genetic origin [4,5]. For more than 95% of uncommon disorders, the US Food and Drug Administration (FDA) has no expressly authorised therapies and overall, only less than 5% of the therapies and palliative care is available to take care of such patients [6]. They generally cause significant mortality and morbidity as they are chronic, progressive, and disabling [7]. Most peculiar diseases are inherited, but at least one in five are also spread through infections, allergies, or environmental factors [8]. Since rare diseases vary in incidence over world, there is no one set definition for such diseases. The European union regulation on orphan medicinal products indicates that RDs are disorders involving 50 per 100,000 individuals in the European population, contrary to the American orphan drug act's classification of RDs as diseases affecting 200,000 people in the United indicates [9-11]. Diagnosing rare diseases are challenging to figure out but even after when the patient is accurately diagnosed with rare genetic disease, they might not have any proper source for treatment of that rare condition instead of addressing the cause, one may wind up turning to therapy meant to treat the underlying disease or only help minimize some of the symptoms [8]. India is the sixth-largest country in terms of total land and the second-largest urban nation in the world. From an evolutionary perspective, a number of migratory waves from Africa have used both land and coastal routes to enter the Indian subcontinent. The country's population is varied in terms of its ethnic, socioeconomic, linguistic, and cultural heritage [12]. The accumulation of detrimental genetic variations has been facilitated by severe inbreeding restrictions, founder effects, and India, a melting pot of genetic diversity. In comparison to other

countries of the globe, India has a higher frequency of autosomal recessive uncommon genetic illnesses due to widespread consanguinity and founder effects in subpopulations. Indian Council of Medical Research (ICMR) has termed a disease as rare if it affects fewer than 1 person in every 2500 people, despite the fact that there are no adequate standard criteria for what constitutes a rare disease in India. The Organisation for Rare Diseases in India (ORDI) has suggested a threshold of 1 in 5000 for the evaluation of rare diseases in India. India has almost no resources dedicated to treating or studying rare diseases, despite the fact that over 70 million individuals are affected by them. Since each rare disease is unique, the population as a whole faces issue that are prevalent throughout the range of rare diseases. This review aims to describe the global public health priority, health care providers and the challenges faced in regard to rare disease.

## Literature Review

### Challenges arising in global public health priority: Rare disease

Due of the difficulties associated with RDs, they have become a global public health concern. For RDs to be better understood, faster diagnosed, and treated, there needs to be unprecedented worldwide integration of RD research. The International Rare Diseases Research Consortium was established in 2011 in order to promote international cooperation between the public and private sectors as well as among stakeholders involved in RDs research from government funding agencies, businesses, academic institutions, and patient advocacy organisations. The three IRDiRC objectives are to

- Diagnose all people with suspected RDs who seek medical attention within a year if the RD has been reported in the medical literature
- Approve 1,000 new treatments for RDs, with the majority focusing on RDs without approved options.
- Place people who are still undiagnosed in an international coordinated diagnostic and research pipeline. They are primarily concerned with the medical requirements of RDs, with the overarching objective of utilising the broad RD belonging for widespread diagnosis and treatment, ensuring that the activities and measures can reach RD patients and families, and posing an expected beneficial impact on the overall well-being and health of the RD population. Research and a global alliance to overcome the socioeconomic issues of the RD people have been encouraged by the Call for UN Resolution. On December 16, 2021, the UN resolution was finally accepted. This is a significant step in raising the RD community's image and securing its support, as it will permit the development of global policies to meet its demands and difficulties. It has previously been very challenging to diagnose due to the heterogeneity and severity of each of the 6,000–8,000 RDs, multisystemic participation, and pleiotropic manifestations.

### Biomarkers associated with rare diseases

Biomarkers are biochemical markers that can identify actual or potential changes in the structure, function, and behaviour of cells, as well as their subcellular partners, in tissues and organ systems. The stage of the disease and the effectiveness and safety of experimental treatments or medications in particular groups may be evaluated using biomarkers. These molecular, genetic, or biochemical indicators offer insights into disease pathogenesis, aid in early detection, enable personalized treatment strategies, and facilitate clinical trials. Currently, a number of methods are being utilised to uncover biomarkers, including network biomarkers, which use extra network data, molecular biomarkers, which use the dynamics of molecular data, and dynamic network biomarkers. Drug development for rare illnesses faces several obstacles, and clinical trial failures are not uncommon. Personalized medicine makes it feasible to detect diseases early, provide a precise diagnosis, and administer specific treatments. For early detection and effective treatment in this respect, the discovery of unusual disease biomarkers is crucial. A biomarker is a biological characteristic that may be scientifically examined and evaluated as an indicator of healthy or unhealthy biological processes. They may improve diagnosis, predict the start of disease, and monitor the efficacy of therapeutic intervention. Novel genes and disease causing mutations are being crucial for discovering meaningful biomarkers because 80% of rare illnesses have genetic origins. Potential biomarkers for rare conditions can be found using current advancements in platform technology for molecular analysis, however few of these candidates have sufficient validation to be incorporated into clinical care regimens for patients. One or a collection of individual molecules can be considered a molecular biomarker if there is a difference in their expression or concentration between a diseased state and a healthy control condition. A molecular biomarker must be able to distinguish between a disease state and a normal state, be reliably detected, and exhibit considerable aberration in a specific condition to be regarded as reliable. The majority of studies has focused on molecular biomarker regulatory networks rather than using the edge or network as a separate biomarker because the use of network biomarkers in rare diseases is still relatively new. Villalba-Benito et al., examined the interaction network of PAX6 during ENS formation to learn more about the aetiology of HSCR. While molecules are crucial for the functioning of cells and are involved in the onset and progression of diseases, complex diseases are frequently influenced more by a group of molecules or a molecular network than a single molecule. The investigation of biomarkers for rare diseases can be improved by networking biomarkers and overcoming the difficulties of collecting samples. Additionally, a single sample's multi-dimensional omics analysis can effectively find network biomarkers. Due to the challenges associated with the diagnosis and treatment of rare diseases, the use of high-throughput sequencing technology and advancements in algorithm development will enable the identification of improved

diagnostic and prognostic biomarkers that will benefit patients with such diseases. Now that illnesses are described at the molecular level, it is possible to find potential therapy targets by identify the metabolic pathways. Due to the small number of individuals with uncommon diseases, it is currently exceedingly challenging to generate a large sample size. National, international, and multi-omics data sharing activities can be used to solve this issue. Another approach to addressing the challenge of small sample size is to use a network technique, which may be used to small or even single data sets, as in a single-sample network. A constraint in diagnosing and treating uncommon diseases is the need for patient-specific therapy for each specialized biomarker. A customised medicine strategy will significantly enhance the standard of treatment provided to patients with rare diseases (Figure 1). The broad disease may be subtyped into more specialised subtypes or subclasses, each of which may be regarded as a rare disease depending on its prevalence and underlying processes. This can be accomplished by using a specific biomarker to establish an increasingly accurate diagnosis. Thus, appropriate biomarker development is crucial for both common and rare diseases.

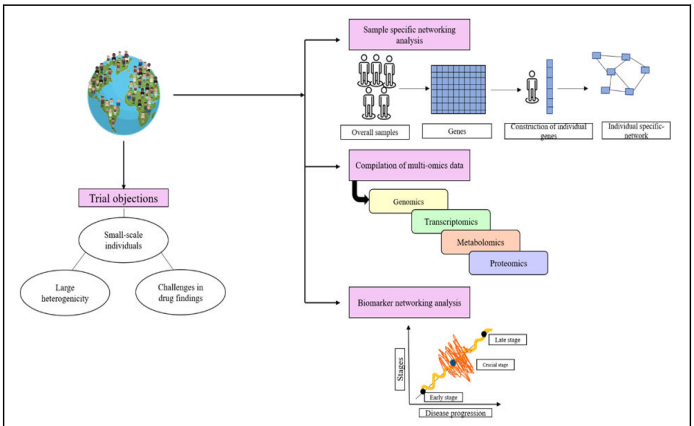


**Figure 1:** Outlook on rare diseases with specific biomarkers

# Discussion

## Challenges related to health care services: Rare disease

Retrospective analysis of 15,258 paediatric emergency room visits showed that 73 visits (0.5%) corresponded to patients with a genetic disorder that was clearly present, but this number is probably underestimated because 2,759 visits (18%) corresponded to patients whose symptoms may have been brought on by an underlying condition. Uncommon diseases made up 3.2% of all hospital admissions in Hong Kong between 2005 and 2016, taking into account the majority of hospital admissions, regardless of age. In contrast, 65.7% of those affected by rare diseases were adults aged 19 or older. According to research, the proportion of patients with genetic abnormalities who were hospitalised five or more times in a year, ten or more times, or twenty or more times, compared to the entire patient population, was 45.4%, 26%, and 12.8%, respectively. In another study, children admitted to hospital in California for birth defects and genetic diseases experienced longer hospital stays, higher hospital costs, and a higher rate of in-hospital mortality (2.7% *vs.* 0.6%) than children hospitalised for other conditions. The cost of living for a patient with rare diseases is quite expensive and for a life time expense will be more depending upon the type of rare diseases like Duchenne Muscular Dystrophy (DMD), fragile X, or haemophilia. Numbers regarding health care services in regard to rare diseases varies from 0.5% to 51%.

## Future aspect: Rare diseases

Early diagnosis is essential, as RDs have a considerable impact on patients' quality of life and socioeconomic burden, according to earlier research, which have focused in particular on these points. RD policies and initiatives are required in the healthcare, social care, insurance, and many other areas in order to create a more socially cohesive community for the RD population. The most thorough screening method for rare diseases is whole genome sequencing. It is important to realise that the physical, social, and economic repercussions of RDs are inextricably linked to a lack of public understanding of rare diseases, medical knowledge, and social support. Rare diseases must improvise like other diseases as study and analysis are conducted. Since 80% of the rare diseases are genetic in origin, they have less amount of cure so in the near future upgrading the diagnostic screening can be taken to next level by analysing more set of genes. Out of 6000-8000 rare diseases in India 450 cases have been reported and have not been clinically treated. Hence, there is no specific treatment for all rare diseases routine management can be a great support for the patients. A key barrier to RD diagnosis delays, in the opinion of more than half of patients and carers, is a lack of medical specialisation, according to the 2019 National Organisation for Rare Disorders (NORD) assessment. Awareness programme on rare diseases should be taken into consideration to the general public in order to know more about the disease condition.

# Conclusion

The aim of the review is to summarize the overall challenges arising in rare diseases with respect to the priority global health and health care services. In addition to their high mortality rates, disabilities, years of life lost, rates of admission or readmission to various hospital settings, rates of admission to long-term care and comfort care settings, and costs of illness, rare diseases are becoming more prevalent and has a negative impact on society. Due to consanguineous marriage traditions and the high incidence of recessive alleles, uncommon illnesses represent a severe burden for the society. By enabling quicker and more precise diagnostics, genomics can significantly reduce the burden of rare diseases. And this also paves the way for incorporating specific biomarkers in exploring between the wide range of rare disease condition in providing more promising and reliable data content for exploring the happening and developmental mechanisms.

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