International Journal of Community Medicine and Public Health
Srivastava V et al. Int J Community Med Public Health. 2024 May;11(5):2107-2115
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20241214

Review Article

An update on management of rare diseases in India

Vivek Srivastava*, Ishika Mohan, Bushra Khatoon

Department of Pharmacology, Amity Institute of Pharmacy, Amity University, Lucknow Campus, Uttar Pradesh, India

Received: 19 March 2024
Accepted: 04 April 2024

***Correspondence:**
Dr. Vivek Srivastava,
E-mail: srivastavav696@gmail.com

ABSTRACT

Rare diseases, characterized by their prevalence in smaller segments of the population, pose significant challenges globally. While definitions may vary across nations based on prevalence rates, these conditions are often life-threatening despite affecting fewer individuals. Genetics play a prominent role, contributing to approximately 80% of rare disorders, with treatments often categorized as 'orphan drugs'. Regardless of a country's economic status or development level, rare diseases impose substantial burdens on healthcare systems and national economies. In India, rare diseases represent a pressing public health concern, yet they often receive inadequate attention and resources. Factors such as insufficient diagnosis, limited awareness, sparse epidemiological data, high treatment costs, and scant research and development exacerbate the challenges faced by patients and healthcare providers. Despite their significant impact, rare diseases remain a neglected area within the healthcare landscape. The aim of this review was to shed light on the rare disease landscape in India by examining available secondary data from published sources. By comprehensively assessing the existing literature, researchers seek to gain insights into the prevalence, management, and challenges surrounding rare diseases in the Indian context. This endeavor is crucial for informing policymakers, healthcare professionals, and stakeholders about the urgent need for improved strategies and resources to address the complex issues associated with rare diseases in India.

Keywords: Rare disease, Orphan drugs, Genetic disorder, National policy

INTRODUCTION

Rare diseases or disorders (RDs) are such conditions which prevail in lower number of people or affect a smaller population as compared to other diseases and disorders. The low prevalence of such diseases is itself a threat for the patients suffering with it as it results in emergence of other factors which hinder its treatment. Countries construct their own definitions for rare diseases considering the figures of prevalence, extent as well as severity of the concerned disease.[1] For instance, according to WHO, rare diseases are the ones which generally deliberate an individual throughout the life and occur in one or less per 1000 people. It has been estimated that there are approximately 6000 to 8000 rare diseases existing in the world and newer rare disorders are adding up to the list on a regular basis.[2] Whereas, about more than 300 diseases are prevalent among these as these affect a large population i.e. 80% of all the patients suffering with these rare diseases.[3]

As per the acknowledged international research, rare diseases have been estimated to have affected about 6% to 8% of a country's population on an average.[4] The list of rare diseases consists of genetic disorders, rare types of cancer, degenerative diseases, infectious tropical disorders, etc.[5] In India rare diseases are classified into 3 types. The People to People Health Foundation (PPHF) organised the Global Rare Disease Conference 2021 in February with cooperation from Niti Aayog, Japan Embassy, Takeda, and state governments to address rare diseases and ensure India's health. The PPHF categorises rare diseases in India into three categories. Treatment options range from organ transplants to nutritional

supplements to life-long enzyme replacement therapies, with costs increasing with age and weight of the child.[6]

The draft classifies diseases into three types: diseases for which proper treatment is available but the treatment is very high and is a lifelong therapy; diseases for which the cost of the treatment is very high but the literature shows favourable outcomes on the patient's life; and diseases for which the cost of the treatment is not a problem but the amount of data available about the treatment is not sufficient which makes it difficult for it to be used as a treatment option for rare diseases.[6]

PATHWAY FOR MANAGING RARE DISEASES

Managing rare diseases is complex due to low awareness and delayed diagnosis. Expertise is often limited to specialized centers, posing access challenges. Treatment decisions are complicated by few options and variable patient needs. Follow-up care is hindered by geographical isolation, impacting patient quality of life. To optimize care, promote multidisciplinary approaches and establish rare disease care networks. Involving patients and families is crucial for knowledge transfer and empowerment. Utilize data from rare disease registries for better understanding and treatment development. Involvement of public authorities is essential for harmonizing care pathways and reducing diagnostic delays. Coordination support systems and active participation from health authorities are critical for facilitating coordinated patient care.[6,7]

INDIAN SCENARIO

India lacks in having a record of population affected with rare conditions. However, if the data present internationally i.e. 6% to 8% is taken into consideration for applying it in India, the estimated number of people will be a significant figure i.e. approximately 72 million to 96 million people. This data though being hypothetical, is still so far the best estimate calculated.

The tertiary hospitals have contributed to record approximately 450 rare disorders and diseases.[7] The list of these rare conditions include sickle cell anaemia, autoimmune disorders, thalassaemia, haemophilia, primary immune deficiency disorders in children, pompe disease, Gaucher's disease, cystic fibrosis, Hirschsprung disease, hemangiomas and various muscular dystrophies. The following factors add to the condition of rare diseases in India.

Unawareness

To study awareness amongst the general population as well as health care professionals, a survey was carried out among 6005 people where 599 responses revealed professionals in healthcare sector had better knowledge about rare diseases compared to others. Among these aware healthcare professionals, about 1/3rd of population had only basic knowledge. However, 3/4th of them had no knowledge about rare diseases and orphan drugs. About 43% of total healthcare professionals had hardly seen any patient of rare diseases and a major percentage of professionals had not seen even a single patient of rare disease disorder in their entire practice journey.[8] It could be thus, concluded from the survey that unawareness which eventually leads to challenges in diagnosis is a most important issue.

Lack of data

The biggest issue faced by the policy makers is the lack of proper data and info about the number of rare diseases existing in India as well as a number of people affected by them.[9] Unless the burden of rare diseases is studied within the Indian population, it is impossible to have an appropriate answer for the policy makers to the question of population suffering with it.

Lower research and development

India did not give the deserved attention to research and development on rare diseases. There is lack of evidence based clinical guidelines too which hinders the development of best practices in health care sectors. Inadequate funding by the government is the chief reason for this.[10]

The Government of India with the help of appropriate incentives and initiatives of export opportunities can encourage the pharma industries for investing in research and development and manufacturing the orphan drugs at lower prices without hindering the quality of drugs.[11]

High cost of orphan drugs and treatment

The market share of orphan drugs is not very significant as there is a small population of people which suffers with rare diseases. Hence, it does not give manufacturers good reasons to invest in manufacturing of orphan drugs. However, the manufacturers still produce these drugs but the selling cost increases many folds in order to compensate the research and development cost, manufacturing and marketing on a large scale with no assurance of market capture.[12] Estimations have revealed that the annual cost of treating a specific rare diseases in a child of ten kg weight, it might cost approximately 18 lacs to 1.7 crores.[13] Also, the methodology for assessing the rare diseases treatment has often been in an experimental phase which slows down the evaluation of clinical relevance as well as cost effectiveness.[14]

Challenges people are facing for accessing treatment for rare diseases

Patients grappling with rare diseases face an array of formidable challenges that significantly impede their access to appropriate care and treatment.

Delayed diagnosis

Foremost among these hurdles is the vexing issue of delayed diagnosis. Owing to the rarity of these diseases and a lamentable lack of awareness among healthcare providers, patients often endure protracted periods of uncertainty before receiving a proper diagnosis. Such delays not only exacerbate the physical and emotional toll on individuals but also compromise treatment efficacy, ultimately jeopardizing patient outcomes.[15]

Limited treatment options

Compounding this predicament is the stark reality of limited treatment options. For myriad rare diseases, there exists a dearth of specific or efficacious treatments, leaving patients grappling with a distressing dearth of therapeutic avenues to manage their conditions effectively.

This dearth not only exacerbates the burden on patients but also underscores the pressing need for accelerated research and development efforts in this domain.[16]

Access to specialized care

Furthermore, accessing specialized care presents a formidable challenge for patients contending with rare diseases. Often necessitating expertise that extends beyond the purview of general practitioners, managing these conditions effectively demands access to specialized centers staffed by clinicians well-versed in the nuances of each ailment. However, such centers of excellence are often sparse, particularly in countries with decentralized healthcare systems, thereby exacerbating the plight of patients who find themselves geographically distanced from the care they so desperately require.[16]

High costs

Economic considerations further compound the tribulations faced by individuals contending with rare diseases. The exorbitant costs associated with the development of treatments for these conditions invariably translate into prohibitively high prices for orphan drugs, rendering them financially inaccessible for many patients. Consequently, individuals are forced to confront the agonizing reality of choosing between financial ruin and vital medical interventions, further underscoring the urgent need for systemic reforms to alleviate this burden.[16]

Lack of awareness

Moreover, the pervasive lack of awareness surrounding rare diseases perpetuates a climate of stigma, misunderstanding, and inertia that impedes timely diagnosis and access to care.

Without adequate public awareness initiatives, patients continue to languish in the shadows, their plight relegated to the margins of medical discourse.[16]

Fragmented healthcare systems

Complicating matters further is the fragmented nature of healthcare systems in many countries, which exacerbates the challenges of coordinating care for patients with rare diseases. The absence of standardized guidelines, national registries, and centralized centers of expertise engenders a landscape rife with inconsistencies, leaving patients at the mercy of a disjointed and often labyrinthine healthcare ecosystem.[16]

Addressing these multifaceted challenges demands a concerted and multifaceted approach encompassing patient advocacy, policy reform, healthcare system strengthening, and intensified research endeavors. By galvanizing these efforts, stakeholders can endeavor to ameliorate the plight of individuals grappling with rare diseases, ushering in an era of enhanced understanding, empathy, and support for those navigating the precarious terrain of rarity and obscurity in the realm of healthcare.

Need for a nationwide policy

In the last few years, approximately 12 to 15 discussions and meetings have taken place in various parts of India in order to evaluate the different issues concerned with rare diseases. It has been proposed by many experts to lay down a well formed regulatory framework.[17] Lacking the same, rare diseases are continuously challenging the patients as well as the health care systems which eventually hinder the development and economic growth of the country. Also (a) it is the responsibility of the state to provide an economic, accessible s well as reliable system of healthcare to each and every citizen; and (b) However, incentivising pharma companies could still not be the only solution. There should be intervention by Government of India to restrict the extravagant cost of the orphan drugs.

Patient advocacy and support

With the increasing discovery and awareness of rare diseases, additional resources must be allocated to research initiatives aimed at better understanding and preventing these conditions. Advocacy groups and collaborative partnerships are crucial in this endeavor, bringing together scientists, pharmaceutical firms, government officials, and policymakers.[18] These groups play a vital role in public policy implementation, research funding allocation, and expediting treatment approvals.[19]

Often formed by family members of affected individuals, rare disease advocacy organizations advocate for the development of public policies and ensure the well-being of patients and caregivers. Examples include the National Organization for Rare Disorders (NORD) in the United States and Rare Diseases International, which operates globally. These organizations work to address the challenges faced by those with rare diseases and advocate for accessible, life-saving treatments worldwide. Additionally, patient advocacy groups worldwide strive to

alleviate challenges and advocate for affordable treatments from both companies and governments.[20]

Patient advocacy groups in India

There are several patient advocacy groups that are currently operating in India. In 2008, Mr. Prasanna Shirol founded the Pompe Foundation, which provides assistance to individuals and families affected by Lysosomal Storage Disorders. Similarly, Mr. Vikas Bhat created the Metabolic Errors and Rare Diseases Organisation of India (MERD), which aims to raise awareness about inborn metabolic errors and neonatal screening. Both of these organizations were established by parents with a child who was affected by the condition they support. Additionally, there are advocacy groups dedicated to Spinal Muscular Atrophy (SMA), Spino-Cerebellar Ataxia (SCA), Duchenne Muscular Dystrophy (DMD), and Osteogenesis Imperfecta. A group of 25 similar organizations came together to form the Organisation for Rare Diseases India (ORDI). This organization is actively involved in assisting patients and their families with the help of NGOs. However, these advocacy groups need to be better organized to gather and share disease, diagnostic, and therapeutic information with afflicted families.[20]

India's diverse regions have unique diseases linked to cultural practices such as endogamy in the North and close proximity in the South.[21] A registry for rare diseases has been created utilizing the data provided by various organizations. This has aided in the reclassification of uncommon diseases based on their incidence in various states.

For instance, diseases such as β-thalassemia are more prevalent in Punjab, Gujarat, West Bengal, Odisha, and Andhra Pradesh, but rare in other states.[22,23] Therefore, they cannot be categorised as rare diseases in these states. Similarly, a house-to-house survey conducted by the Molecular Diagnostics, Counselling, Care, and Research Centre (MDCRC) Coimbatore suggests that Duchenne Muscular Dystrophy is a common illness in Tamil Nadu and cannot be classified as rare.[24] Such data must gradually be merged so that advocacy groups can focus their efforts on rare diseases and help establish a comprehensive and factual National registry, which would further aid in creating the National Policy for Rare Diseases.[25,26]

Initiatives in India

The past few years of this decade have shown noteworthy development in the regards which may prove to bring changes in the healthcare sector of India. First and foremost, 6th February 2013 markedthe launch of National Health Program for Children translated to *Rashtriya Bal Swasthya Karyakam* in hindi was the first step of its kind. This scheme covered about 270 million children. Individuals from the from their birth up to 18 years of age were meant eligible for this scheme. The program was structured to work in different phases and move towards the objective of universal health coverage. The program was framed to perform screening of almost 30 health conditions concerned with children which included numerous congenital defects, disorders & diseases, deficiencies, vision and hearing impairment, malfunctioning of neuro-motor system, delayed motor function, cognitive and lingual impairment, autism, ADHD.

Another important development recorded in India was changed disease pattern from nutritional deficiency disorders to prevalence of communicable diseases. Organisation for Rare Diseases India (ORDI) is expected to have a major role for carrying out transformation in trends of RDs in India. ORDI is a non-profit umbrella organisation constituted for rare diseases and patients of rare diseases in India which aims at raising awareness, advocating public policies, encouraging pharmaceutical and biotech industries to research and develop drugs for rare diseases management. In the year 2019, the Governmentt of India brought '*Ayushman Bharat Pradhan Mantri Jan Arogya Yojna*' which aimed at providing free medical assistance to the citizens of India who were underprevilliged and fulfilled the requirements to avail the provisions of the policy. It was an initiative to help 40% of Indians in regards to health.[8]

Table 1: Table showing major institutes in India working on rare diseases and disorders.[8]

Institutes	Area of research
All India Institute of Medical Sciences, Jodhpur	Cystic fibrosis, leucocyte adhesion defect, etc.
All India Institute of Medical Sciences (AIIMS), New Delhi	Skin disorders, mitochondrial disorders, neurological disorders, cardiac disorders, developmental disorders, and pediatric disorders.
Amrita Institute of Medical Sciences and Research Centre, Cochin	Lysosomal storage disorders (LSDs), Werner syndrome
CSIR Central Drug Research Institute (CDRI), Lucknow	Progressive external ophthalmoplegia
CSIR Centre for Cellular and Molecular Biology (CCMB), Hyderabad	Mitochondrial disorders, hemoglobinopathies
Centre for Human Genetics (CHG), Bengaluru	Inherited metabolic diseases (IMDs), EB, lysosomal storage disorders

Continued.

Institutes	Area of research
Center for Genetic Studies and Research, MMM Hospital, Chennai	Rare chromosomal disease
FRIGE's Institute of Human Genetics, Ahmedabad	Hemoglobinopathies, musculopathies, neurodegenerative diseases, lysosomal storage disorders, among other genetic diseases
CSIR Indian Institute of Chemical Biology (IICB), Kolkata	Oculocutaneous albinism (OCA), Wilson disease (WD), autism
Indian Institute of Science (IISc), Bengaluru	Primary microcephaly, anencephaly, Parkinson's disease, Wilson disease, and neuromuscular disorders
Indira Gandhi Institute of Child Health, Bangalore	Lysosomal storage disorders, Prader-Willi syndrome, and skeletal dysplasia, among other rare disease
CSIR Institute of Genomics and Integrative Biology (IGIB), New Delhi	rare genetic diseases including skin disorders, ataxias, cardiac disorders, neurological disorders, primary immunodeficiency disorders, endocrinology disorders, nephrological disorders, mitochondrial disorders, Wilson disease, hemoglobinopathies, lysosomal storage disorders, and developmental disorders, etc.
Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry	Werner syndrome, Fanconi anemia, split hand-split feet syndrome, skin disorders, incontinentia pigmentia.
JK Lone Hospital, SMS Medical College, Jaipur	Ectodermal dysplasias, skeletal dysplasias, neurological disorders, lysosomal storage disorders, and coagulation disorders, etc.
King Edward Memorial (KEM) Hospital, Mumbai	Hemoglobinopathies, LSDs, congenital metabolism disorders.
Manipal University, Manipal	Skeletal dysplasia, neurodegenerative diseases, metabolic disorders, bleeding disorders, and malformation syndromes, etc.
Maulana Azad Medical College, New Delhi	LSDs, skeletal dysplasia, hemophilia, pediatric disorders.
National Institute of Biomedical Genomics (NIBMG), Kalyani	Hemoglobinopathies, Wilson disease, DMD, eye disorders
National Institute of Mental Health and Neuro-Sciences (NIMHANS), Bangalore	Rare neuromuscular disorders including limb girdle muscular dystrophy, amyotrophic lateral sclerosis, metabolic myopathies, rare congenital myasthenic syndromes, neuropsychiatric syndromes, sickle cell anemia, mitochondrial disorders, and metabolic disorders.
Nizam's Institute of Medical Sciences, Hyderabad	LSDs, hemoglobinopathies, and neurodegenerative disorders, etc.
Osmania University, Hyderabad	Rare chromosomal disorders
Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh	Immune diseases, bone diseases, Wilson diseases, etc.
Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow	LSDs, oro-facial-digital syndromes, neurodevelopment disorders, hemoglobinopathies, neurodegenerative disorders, and metabolic disorders, etc.
Sir Ganga Ram Hospital, New Delhi	LSDs, neurodegenerative disorders, IEMs, mitochondrial disorders, etc.
The Centre for DNA Fingerprinting and Diagnostics (CDFD), Hyderabad	Neuromuscular disorders, metabolic diseases, hemoglobinopathies, thrombotic disorders, triplet repeat disorders, LSDs, etc.

Table 2: Table showing various organizations in India providing assistance to patients of rare diseases and disorder.[27]

Organizations	Web address
Alzheimers and Related Disorders Society Of India (ARDSI)	http://ardsi.org
Birth Defects Registry of India	http://www.fcrf.org.in/bdriabus.asp
Down Syndrome Federation India	http://downsyndrome.in/

Continued.

Organizations	Web address
Fragile X Society–India	http://www.fragilex.in
Genetic Alliance	http://www.geneticalliance.org
Hemophilia Federation	http://www.hemophilia.in/
Indian Rett Syndrome Foundation	www.rettsyndrome.in
Indian Association of Muscular Dystrophy	www.iamd.in
Indian Prader-Willi Syndrome Association	https://ipwsa.in/
Indian Patients Society for Primary Immunodeficiency (IPSPI)	www.ipspiindia.org
Indian Organization for Rare Diseases (I-ORD)	http://www.i-ord.org/
Indian Society for Primary Immune Deficiency	http://www.ispid.org.in/
Lysosomal Storage Disorders Support Society (LSDSS)	www.lsdss.org
Metabolic Errors and Rare Diseases (MERD)	http://merdindia.com
Muscular Dystrophy Association India	http://mdindia.net/
Muscular Dystrophy Foundation India	http://www.mdfindia.org
National Thalassemia Welfare Society	http://www.thalassemiaindia.org/
Open Platform for Rare Diseases (OPFORD)	https://opford.org/
Organization of Rare Disorder India (ORDI)	https://ordindia.in/
Pompe Foundation	http://pompeindia.org/
Rare Diseases India	http://www.rarediseasesindia.org
Retina India	http://retinaindia.blogspot.com/
Sjogren's India	http://www.sjogrensindia.org
Society for Hemophilia Care, India	http://www.shcindia.org/
Thalassemics India	www.thalassemicsindia.org

ESTABLISHMENT OF NATIONAL POLICY

Strong efforts were made to address these issues in the year 2014 followed by 2017. The Government of India proposed a documented 'National policy for treatment of rare disease' in India. The document outlined the several steps for dealing with rare diseases as well as it mentioned the requirement of a reserved fund of 100 crores by the central as well as state government in order to bring the policy into existence and its working.

This policy, introduced in 2017, was taken for revision by government of India in 2018. The government instructed for a committee of ten members to review the policy. The committee was constructed to review the policy, frame a definition of rare diseases in India as well as structure a new national policy. There were three chief committees made for the same, the committees and the appointed members were. Professor V. K Paul Committee, Head at the department of Pediatrics, AIIMS, New Delhi. This committee worked on 'Prioritisation of therapy for rare genetic disorders'.

Professor I. C Verma (sub-committee), Director, Institute of Medical Genetics and Genomics at Sir Ganga Ram Hospital. This committee framed guidelines for 'Therapy and Management'.

A powerful interdisciplinary committee for rare diseases was also made with Dr. Deepak K Tempe being the Chairperson. Dr. Tempe is dean of Maulana Azad Medical College, New Delhi

COMMITTEE REPORTS

The V. K. Paul committee

It reported the 'Prioritisation of therapies for rare diseases'. The report comprised of elaborated work on therapies available for genetic disorders, both one time as well as long-term cost of therapies, evidence based clinical results, prioritization of genetic diseases, quality of life and the present guidelines. It was recommended by the committee to provide informative genetic counselling to families as well as to provide them with parental screening of genetic disorders in order to keep them aware of producing a child with genetic defect.

The I. C. Verma sub-committee

This committee made a comparative study of Indian and global parameters for rare diseases such as the burden of diseases and definition of rare diseases. Drug availability, available treatments and its cost estimation, evidence-based results of these treatments were also included in the study. It made recommendations for the Government of India to intervene in developing a funding system for rare diseases treatment and a national policy for rare diseases.

D. K. Tempe committee

The various factors of RDs as a public health issue such as the exorbitant prices of RDs treatment, priorities of common diseases over RDs in public health and allocation of resources accordingly, lack of prevalence data,

inadequate diagnosis and restricted treatment were considered by this committee.

Hence, the committee made recommendations for the national policy to include a treatment strategy which works in a phased manner and give priority to rare genetic diseases with existing good clinical results.[28]

POLICY RECOMMENDATION

The three committees framed a number of recommendations for structuring and national policy for treatment of rare diseases. Apart from funding several other recommendations with a holistic approach for management of RDs was kept forward by these committees with focus on creating awareness, prevention, R and D with regards to drugs and treatment, diagnosis, training, production of orphan drugs and its availability at reasonable prices, insurance etc.

Since, an effective management requires comprehension as well as contribution of several sectors which work interdependently with the same intention therefore, the recommendations for RD management became a part of several departments and ministries.

NATIONAL POLICY FOR TREATMENT OF RARE DISEASES (NPTRD) 2020

The amendment of National Policy 2017 was done and drafted by Govt. Of India in January, 2020 as 'National Policy for Treatment of Rare Diseases'. The key features of this policy are as follows: (a) the ICMR will be constituting a registry for patients of rare diseases; (b) as per this policy, RDs comprise of genetic disorders, rare type of cancers, generative diseases and infectious tropical diseases; (c) this policy has categorised RDs into three major class based on the type and duration of treatment. These are diseases with one-time curative treatment, long term treatment with low cost, and long term treatment where treatment cost is high; (d) as per this policy, under the scheme of "*Rashtriya Arogya Nidhi*" patients suffering with rare conditions which require a one-off curative treatment will be getting compensation of 15,00,000 INR. This provision is restricted to the recipients of '*Pradhan Mantri Jan Arogya Yojana'*, (e) in accordance to this policy specific medical institutes are planned to get the certification of 'Centre of excellence for rare diseases'. The list of these institutes includes King Edward Medical College, Mumbai; Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow; All India Institute of Medical Sciences, New Delhi and 4 others; (f) it also covers several diseases whose annual treatment cost is estimated to range from ten lakh INR to one crore INR. These diseases are Gaucher's disease, Hurler syndrome, Wolman disease, etc for which digital platforms are supposed to be established in order to raise corporate fundings as well as donations; and (g) in administrative committee is also aimed by this policy to develop guidelines which could determine the diseases that need funding.[29]

PRaGeD: A BEGINNING TOWARDS A NATIONAL MISSION PROGRAMME

The PRaGeD program in India focuses on rare genetic disorders in children, marking a significant advancement in healthcare. It raises awareness among healthcare professionals and the public, improves diagnosis and treatment, and discovers unique genetic variations in the Indian population. Utilizing next-generation sequencing techniques, PRaGeD aims to uncover novel genes and variants associated with rare diseases prevalent in India. Unlike hypothesis-driven programs, PRaGeD relies on years of genetic testing and research experience. It plans to enroll 5000 families for comprehensive genomics studies, creating essential databases for global researchers. This initiative not only advances personalized medicine but also accelerates the development of new medicines, diagnostic tools, and screening tests for genetic illnesses. With modern sequencing technology and government support, India is poised to make significant strides in rare disease detection and treatment, promising better care for affected individuals.[30]

DEVELOPING THERAPIES FOR RARE DISEASE MANAGEMENT

Given the difficulties that patients with rare diseases have in receiving appropriate treatments, it is critical that therapies be developed and manufactured in India. A complete strategy to drug development, emphasising the importance of establishing patient registries, developing local natural history models, and generating innovative therapeutic compounds that are both effective and inexpensive. Furthermore, the emphasis is on the significance of creating Indian skills for producing rare illness medications domestically to ensure availability at competitive pricing.[31]

Exon-skipping therapy appears as a noteworthy therapeutic route discussed in the study. This method, which modifies mRNA splicing to make functional proteins, has the potential to treat illnesses such as Duchenne muscular dystrophy (DMD) and spinal muscular atrophy. Significant progress has been achieved in this field, including the invention of a patented process for manufacturing morpholino-based antisense oligonucleotides (ASO). Researchers have successfully addressed issues linked to increasing cell entrance efficiency, advancing the practicality of exon-skipping treatment for clinical use.[32]

The primary focus of rare disease drug development is on various forms of gene therapy. Gene therapy offers a viable therapeutic option without the need for knowledge of disease causes, as the underlying pathogenic mechanisms are unclear.[33] Gene therapy has emerged as a major emphasis in the development of treatments for rare diseases, with over 100 trials using adeno-associated virus (AAV)-based systems now underway. The construction of a viral AAV-based gene therapy platform highlights the

need of developing robust safety standards and ensuring regulatory compliance to assist clinical trial progression.[34,35] New and promising technologies such as mRNA therapeutic platforms and non-viral nanoparticle-based gene systems for delivery offer innovative treatment options. The medicinal advantages of mRNA are highlighted, citing its effective use in COVID-19 immunization and its favorable safety record.[36] Additionally, researchers have developed a non-viral nanoparticle-based gene delivery technology that offers benefits such as low toxicity and the ability to be dosed repeatedly.[37] Gene editing technologies, such as CRISPR/Cas systems, possess substantial potential for rectifying genetic abnormalities at their core. The unveiling of a novel gene-editing system employing an engineered FnCas9 enzyme signifies a notable advancement, notwithstanding the hurdles encountered in its transition to clinical efficacy.[38]

Despite these advancements, navigating the drug approval process in India presents a significant hurdle, particularly for rare genetic disorders. Chirmule et al delineate the regulatory landscape for orphan diseases, emphasizing the need for greater awareness among drug developers to facilitate smoother approval pathways.[39] Addressing the challenges of rare illness medication development would require a collaborative effort that combines scientific innovation, regulatory support, and the construction of localised manufacturing capabilities. Ongoing research and collaboration have the potential to greatly improve the quality of life for those suffering from these severe illnesses.[40]

CONCLUSION

In India, rare diseases pose significant challenges characterized by delayed diagnosis, limited treatment options, and high costs, exacerbating the burden on affected individuals and families. While the government has initiated steps like establishing a rare disease registry and designated centers of excellence, a comprehensive national policy is essential to address the multifaceted aspects of rare disease management. Initiatives such as the National Policy for Treatment of Rare Diseases 2020 and the PRaGeD program signify positive strides, yet persistent hurdles in drug approvals, research funding, and local manufacturing capabilities impede progress.Patient advocacy groups play a crucial role in raising awareness, influencing policy formulation, and providing support to affected individuals. Fostering local research endeavors is paramount in developing novel treatments and enhancing understanding of rare diseases within the Indian context. While promising advancements have been made, sustained efforts are necessary to navigate regulatory complexities, secure adequate funding, and build local research capacities. By prioritizing collaborative approaches, leveraging existing initiatives, and fostering a supportive ecosystem, India can strive towards more effective management and improved outcomes for those grappling with rare diseases nationwide.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Richter T, Nestler-Parr S, Babela R, Khan ZM, Tesoro T, Molsen E, et al. Rare Disease Terminology and Definitions-A Systematic Global Review: Report of the ISPOR Rare Disease Special Interest Group. Value Health. 2015;18(6):906-14.
2. Bali RK, Bos L, Gibbons MC, Ibell S. Rare Diseases in the Age of Health 2.0. Springer: Berlin; 2014: 2191-3811.
3. Gainotti S, Torreri P, Wang CM, Reihs R, Mueller H, Heslop E, et al. The RD-Connect Registry & Biobank Finder: a tool for sharing aggregated data and metadata among rare disease researchers. Eur J Hum Genet. 2018;26(5):631-43.
4. Giannuzzi V, Conte R, Landi A, Ottomano SA, Bonifazi D, Baiardi P, et al. Orphan medicinal products in Europe and United States to cover needs of patients with rare diseases: an increased common effort is to be foreseen. Orphanet J Rare Dis. 2017;12(1):64.
5. Šimerka P, Eur-LEX A. Council recommendation of 8 June 2009 on an action in the field of rare diseases. Off J Eur Union. 2019;2009:7-10.
6. India Health. Rare diseases: All about treatment, challenges, and why should India take them seriously, 2021. Available at: https://www.india.com/health/rarediseasesallabouttreatment-challenges-and-why-should-indiatakethem-seriously-4547527/2021. Accessed on 27 October 2022.
7. CPHI. Rare diseases care pathway: A major challenge to harmonize patient management, 2021. Available at: https://www.cphi-online.com/rarediseasescarepathwayamajorchallenge-tonews114462.html. Accessed on 27 October 2022.
8. Bhattacharya SU, Katoch VM, Majumdar P, Bhattacharya A. Rare diseases in India: current knowledge and new possibilities. Proc Indian Natl Sci Acad. 2016;82(4):1183-7.
9. Agrawal R, Rao MA, Chowdary GKB, Gayatri K, Rao KM, Rao SP, et al. Baseline knowledge of rare diseases in India- a survey. Int J Rare Dis Disord. 2019;2(1):4-11.
10. Mohanty R, Barick U, Gowda A, Nair A, Mital S, Patil A. Scope for Patient Registries in India. IJMRHS. 2016;5(4):58-61.
11. The Quint. An ordinary life with a rare disease: battle for drug discovery, 2018. Available at: https://www.thequint.com/fit/gnemyopathybattlewith-rare-disease. Accessed on 01 March 2024.
12. Shire H. Rare disease impact report: Insights from patients and the medical community. J Rare Disord. 2013;26:10.
13. Schulenburg GJM, Frank M. Rare is frequent and frequent is costly: rare diseases as a challenge for

health care systems. Eur J Health Econ. 2015;16(2):113-8.
14. Taneja A, Shashidhara LS, Bhattacharya A. Rare diseases in India: Time for cure-driven policy initiatives and action. Curr Sci. 2020;118(1500):1500-6.
15. Choudhury MC, Saberwal G. The role of patient organizations in the rare disease ecosystem in India: an interview based study. Orphanet J Rare Dis. 2019;14(1):117.
16. Schieppati A, Henter JI, Daina E, Aperia A. Why rare diseases are an important medical and social issue. Lancet. 2008;371(9629):2039-41.
17. EURORDIS. Rare Diseases Europe. About Rare Diseases, 2016. Available at: https://www.eurordis.org/information-support/what-is-a-rare-disease/. Accessed on 08 March 2024.
18. Hughes DA, Poletti-Hughes J. Profitability and Market Value of Orphan Drug Companies: A Retrospective, Propensity-Matched Case-Control Study. PLoS One. 2016;11(10):e0164681.
19. Merkel PA, Manion M, Gopal-Srivastava R, Groft S, Jinnah HA, Robertson D, et al. The partnership of patient advocacy groups and clinical investigators in the rare diseases clinical research network. Orphanet J Rare Dis. 2016;11(1):66.
20. Choudhury MC, Saberwal G. The role of patient organizations in the rare disease ecosystem in India: an interview based study. Orphanet J Rare Dis. 2019;14(1):117.
21. Song P, Gao J, Inagaki Y, Kokudo N, Tang W. Rare diseases, orphan drugs, and their regulation in Asia: Current status and future perspectives. Intractable Rare Dis Res. 2012;1(1):3-9.
22. Bhattacharya Y, Iyer G, Kamireddy AP, Poornima S, Juturu KK, Hasan Q. Rare disease advocacy groups and their significance in diagnosis, management, treatment, and prevention of rare diseases. Intech Open. 2019.
23. Tamang R, Singh L, Thangaraj K. Complex genetic origin of Indian populations and its implications. J Biosci. 2012;37(5):911-9.
24. Colah R, Italia K, Gorakshakar A. Burden of thalassemia in India: the road map for control. Pediatr Hematol Oncol. 2017;2(4):79-84.
25. Murugan S, Chandramohan A, Lakshmi BR. Use of multiplex ligation-dependent probe amplification (MLPA) for Duchenne muscular dystrophy (DMD) gene mutation analysis. Indian J Med Res. 2010;132:303-11.
26. Khosla N, Valdez R. A compilation of national plans, policies and government actions for rare diseases in 23 countries. Intractable Rare Dis Res. 2018;7(4):213-22.
27. Taneja A, Shashidhara LS, Bhattacharya A. Rare diseases in India: Time for cure-driven policy initiatives and action. Curr Sci. 2020;118(1500):1500-6.
28. Sivasubbu S, Scaria V. Genomics of rare genetic diseases- experiences from India. Hum Genom. 2019;13(1):1-18.
29. MOH. National Policy for rare diseases, 2021. Available at: https://main.mohfw.gov.in/sites/default/files/Final%20NPRD,%1. Accessed on 28 January 2022.
30. Kar AS, Dalal A. Rare genetic diseases in India: Steps toward a nationwide mission program. J Biosci. 2024;49:34.
31. Patel N, Pandya H, Sangle G, Choudhury MC. Enhancing access to treatment for Gaucher disease in India: The need for indigenous manufacturing. J Biosci. 2024;49:38.
32. Patel N, Pandya H, Sangle G, Choudhury MC. Enhancing access to treatment for Gaucher disease in India: The need for indigenous manufacturing. J Biosci. 2024;49:38.
33. Anguela XM, High KA. Entering the Modern Era of Gene Therapy. Annu Rev Med. 2019;70:273-88.
34. Raghu P, Sharma Y, Suseela Devi ABN, Krishnan H. Challenges and opportunities for discovering the biology of rare genetic diseases of the brain. J Biosci. 2024;49:26.
35. Selot R, Ghosh A. Recent developments in gene therapy research in India. J Biosci. 2024;49:37.
36. Iyer VR, Kaduskar BD, Moharir SC, Mishra RK. mRNA biotherapeutics landscape for rare genetic disorders. J Biosci. 2024;49:33.
37. Rao D, Ganguli M. Non-viral delivery of nucleic acid for treatment of rare diseases of the muscle. J Biosci. 2024;49:27.
38. Bhattacharyya P, Mehndiratta K, Maiti S, Chakraborty D. Rare genetic disorders in India: Current status, challenges, and CRISPR-based therapy. J Biosci. 2024;49:28.
39. Chirmule N, Feng H, Cyril E, Ghalsasi VV, Choudhury MC. Orphan drug development: Challenges, regulation, and success stories. J Biosci. 2024;49:30.
40. Bhattacharya A, Bhattacharya S, Mishra R. Current status of research in rare genetic disorders and drug discovery in India. J Biosci. 2024;49:39.

Cite this article as: Srivastava V, Mohan I, Khatoon B. An update on management of rare diseases in India. Int J Community Med Public Health 2024;11:2107-15.