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Comprehending Rare Diseases in India: Uncommon Challenges and Hope from a Perspective

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Abstract

Rare Diseases (RDs), also referred to as orphan diseases, are illnesses that only afflict a tiny portion of the general population. Although these conditions are uncommon on their own, they affect a sizable population globally when combined. Patients, their families, and the healthcare system have particular difficulties when dealing with rare diseases. RDs encompass infectious tropical diseases, degenerative diseases, rare malignancies, and genetic disorders. Due to the multitude of country-specific definitions of RD, there is currently no widely agreed description of what an RD is. Given that RD typically affects 6-8% of the population in any given nation, even a conservative estimate for India's 1.4 billion inhabitants would come out to be approximately 90 million. Scientists, activists, decision-makers and non-profit organizations have worked very hard in the last few decades to address the primary issues surrounding RDs, from treatments to diagnostics. Despite their best efforts, unfortunately, only a tiny percentage of RDs have access to effective treatments at this time. However, the speed at which genomic sequencing technology and international data exchange have developed has accelerated the field of precision medicine. This has sped up the identification of new RDs and made it simpler to evaluate genetic heterogeneity in RDs that may affect the severity of the disease and the response of the patient to particular pharmaceutical therapies. While the field of orphan drug development has advanced significantly, much more work needs to be done to guarantee equitable use of genetic therapies. To improve our understanding and treatment of RDs, cooperation between pharmaceutical companies, researchers, and healthcare providers is crucial. We can work to enhance the lives of people impacted by RDs by raising awareness, supporting inclusivity, and encouraging research.

Introduction

Rare Diseases (RDs), also referred to as orphan diseases, are illnesses that only afflict a tiny portion of the general population [1-3]. Although these conditions are uncommon on their own, they affect a sizable population globally when combined. Living with a RD poses unique challenges for patients, their families, and the healthcare system. Improper management of the condition can have fatal consequences for the patient's health [4,5]. The number of RDs is thought to range from 6000 to 8000 world-wide, and new cases are frequently documented in the medical literature [3]. RDs include genetic diseases, rare cancers, infectious tropical diseases, and degenerative diseases [6,7]. Eighty percent of RDs have a genetic basis and mostly manifest in early life [8]. Long-term absences from work or school have been reported by a growing number of individuals with RD due to its severity [4].

Understanding rare diseases in India

Due to the multitude of country-specific definitions of RD, there is currently no widely agreed description of what an RD is [9,10]. A disease is generally considered "rare" when it affects <1:2,000 people (i.e., <0.05%) in the European Union and <1:200,000 people (i.e., <0.0005%) in the USA [1]. It's interesting to note that a certain disease may be considered rare in one geographical area but not necessarily in another because of the varying effects of specific

genetic, environmental, and demographic factors [7,11]. India must therefore carefully evaluate the prevalence and severity of the RDs before coming up with a definition that meets her needs. Having said that, in India, a disease is generally regarded as rare if it affects less than 1 in 2,500 people [12]. Given that RD typically affects 6-8% of the population in any given nation, even a conservative estimate for India's 1.4 billion inhabitants would come out to be approximately 90 million. The fact that there are currently few epidemiological data on RDs in India in terms of prevalence rate further complicates our understanding of RDs in that country. In order to combat this, the Indian Council of Medical Research (ICMR) has launched a hospital-based "National Registry for Rare Diseases" with the assistance of institutions across the country that are engaged in the diagnosis and treatment of RDs [13]. Additionally, in March 2021, the Ministry of Health and Family Welfare, Government of India, approved the National Policy for Rare Diseases 2021 (NPRD), a public policy document. More importantly, diagnostic efficiency is also a major factor in the classification of RDs, as many patients with RD may go undetected due to the nature of diagnostic tools, and the likelihood of incomplete knowledge regarding some RDs [13]. Despite numerous obstacles, innovative approaches have also been employed in an effort to speed up the diagnosis of RDs in India. For instance, the goal of the Genomics for Understanding Rare Diseases: India Alliance Network (GUARDIAN) is to provide a special framework for healthcare delivery, implementation, and planning that is tailored to RD [12].

Therapeutic challenges associated with rare diseases

Scientists, activists, decision-makers, and nonprofit organizations have worked very hard in the last few decades to address the primary issues surrounding RDs, from treatments to diagnostics. Despite their best efforts, unfortunately, only a tiny percentage of RDs have access to effective treatments at this time [14,15]. Nevertheless, rapid genomic sequencing technology and extensive worldwide data exchange have significantly sped up the discovery of new RDs [16,17]. With the significant progress made in whole-genome sequencing (WGS) in recent years, a critically ill child with an RD can be diagnosed in few hours. Additionally, the unparalleled progress of WGS has contributed to the rapid development of precision medicine by making it simple to evaluate the genetic heterogeneity in an RD that might affect the severity of the disease and how well a patient responds to a certain pharmaceutical therapy [18,19]. Research on natural history plays a major role in the epidemiological comprehension of RDs [20-22]. These studies follow RD of a patient across time to find genetic, environmental, demographic and/or epigenetic factors that are associated with the development and prognosis of the disease in the absence of treatment. Additionally, they have produced valuable data regarding the phenotypic variety of RDs and have identified subgroups of RDs that may result from distinct genetic variants and cause comparable disease symptoms [23]. Therefore, when an Research and Development (R&D) organization wants to apply for more extramural funding for its R&D from public or private funding organizations, such longitudinal studies should be given top attention. Similar long-term investigations might potentially provide insight into the outcomes of the treatments.

Because it takes a lot of research to develop orphan drugs, they are typically quite expensive [24-26]. Furthermore, wealthy individuals are largely able to purchase these extremely expensive treatments due to the narrow consumer base for orphan drugs. Interestingly, though, patients may receive up to USD 27,000 in financial assistance for RD treatment as a one-time therapy expense under India's NPRD, 2021 [27]. Moreover, building a knowledge basis for prevention or effective treatment of RDs requires the identification of underlying mechanisms, particularly for unusual cases of RDs. For instance, a single gene may have several distinct mutations that cause different diseases with different symptoms or intensities [28-30]. After being categorized as a single disease for a long time, muscular dystrophy is now known to have nine main variants, with Duchenne Muscular Dystrophy (DMD) being the most prevalent type [31-33]. It is unclear if epigenetic factors-aside from genetics-have a significant impact on the genesis of many RD types. Therefore, it is necessary to include epigenomics in a routine RD screening program because it is becoming increasingly important in research studies attempting to understand the underlying mechanisms of very uncommon RD [34,35]. Epigenomics involves studying the entire set of epigenetic modifications on a cell's genetic material. Together, in order to expedite the development of early-stage possible therapeutic interventions, comprehensive WGS and epigenomics should be included in the three-pronged screening procedure for any RDs, along with targeted polymerase chain reaction (PCR) screening for known gene mutations [36].

Complex regulatory challenges and potential fixes pertaining to the orphan drug approval procedure

One area of public health policy intricacy that necessitates careful consideration is the determination of whether data is sufficient for the regulatory agency to approve drugs intended for individuals with RD [37,38]. In general, companies have significant financial and time constraints when producing the evidence necessary to justify the licensing of a drug, particularly biologics. Additionally, preliminary clinical studies may not confirm the safety or efficacy of the orphan drug. Given the challenges of carrying out traditional clinical trials for many extremely RDs, including those with clinical features that progress over a longer period of time, this is further complicated by the fact that different standards of evidence should be applied to approve orphan drugs [39,40]. Consequently, the lack of patients known to have the disease indication makes it challenging to definitively verify the safety and efficacy of orphan medications, especially when the clinical improvement is marginal, utilizing a relatively low-powered clinical trial. Furthermore, because of the small market and the higher expenses associated with a new drug's necessary regulatory compliance, orphan pharmaceuticals-drugs meant for very rare populations-may be especially susceptible to extinction [41]. Having said that, in order to get around this, the Orphan Drug Act was put into effect in the United States [42]. It offers biopharmaceutical companies protection from competition in the form of grant support, tax exemptions for specific clinical

development costs, exclusive marketing rights and other various incentives to develop drugs for people with RD. A rolling review mechanism must be used to expedite the approval of new RD drug applications, and a special category must be established to do so [43]. This will enable periodic consultation with regulatory bodies like the Drug Controller General of India (DCGI) regarding the entire application for approval, including sections on pre-clinical studies, early phase I and phase II clinical trial results, and phase III studies [44]. An expedited drug approval procedure that permits the use of surrogate endpoints-biomarkers meant to replace clinical endpoints-to predict clinical benefit in certain situations, including urgent need, would encourage pharmaceutical companies to focus more on developing orphan disease treatments [45]. Additionally, the drug sponsor benefits from looser regulations for post-marketing research to gather more information about the advantages and disadvantages of a medicine. Therefore, a combination of "push" and "pull" incentives from the regulatory agencies would facilitate the orphan drug development process overall [46]. The entire process from drug development to market approval and authorization is likely to be facilitated by push incentives like lowering or subsidizing R&D costs, providing research tax credits, grants for orphan products and exemption from user fees, and pull incentives like the market exclusivity provision and expedited and facilitated drug review processes.

Although the biopharmaceutical sector, public companies, and private foundations have placed a great deal of focus on accurately investigating RDs and developing orphan drugs, approximately 95% of RD cases still lack suitable treatment [47,48]. To circumvent this, the development of cellular, genetic and molecular therapies could power precision medicine, which would transform the healthcare sector and enable patients with RD to be managed effectively. For instance, skin biopsies make it simple to develop patient-derived fibroblast cell cultures [49,50]. These cellular models are particularly helpful in understanding the pathophysiological changes and how a certain mutation reacts to a given treatment. To gain a deeper understanding of the underlying mechanisms of RDs, it is also conceivable to produce two of the most affected cell types, such as neuron and muscle, using current direct or indirect cell trans-differentiation procedures [51,52]. Therefore, these cellular models can be used by precision medicine, which typically relies on the assumption that distinct mutations and notable inter-individual genetic variation significantly contribute to a particular drug response, to test the toxicity and efficacy of candidate orphan drugs and select the most effective one to meet a patient's needs [53,54].

Even while the field of developing orphan drugs has made significant strides, much more has to be done to ensure that genetic therapy is used equitably. Genomic medicine carries a risk due to the time-consuming nature of genetic teaching and counseling: Some physicians may find it difficult to recognize the true benefits and may grow reticent to suggest genetic testing or therapy [55,56]. Incorporating scientists and clinical geneticists into a multidisciplinary, case-based approach could help health care practitioners make more useful decisions for their patients. Moreover, genomic medicine should be a regular topic of discussion at all CMEs (continuing medical education) across the globe [57].

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Competing interests

The authors have no competing interests.

References

1. Danese E, Lippi G (2018) Rare diseases: The paradox of an emerging challenge. Ann Transl Med 6(17): 329.
2. Field MJ, Boat TF (2010) Rare Diseases and orphan products: Accelerating research and development. Institute of Medicine (US) Committee on accelerating rare diseases research and orphan product development. Washington (DC): National Academies Press (US), 1, Introduction.
3. Haendel M, Vasilevsky N, Unni D, Bologa C, Harris N, et al. (2020) How many rare diseases are there? Nat Rev Drug Discov 19(2): 77-78.
4. Witt S, Schuett K, Wiegand GS, Boettcher J, Quitmann J (2023) Living with a rare disease - experiences and needs in pediatric patients and their parents. Orphanet J Rare Dis 18(1): 242.
5. Vonder LC, Diesen PS, Feragen KB (2017) Living with a rare disorder: A systematic review of the qualitative literature. Mol Genet Genomic Med 5(6): 758-773.
6. Angural A, Spolia A, Mahajan A, Verma V, Sharma A, et al. (2020) Review: Understanding rare genetic diseases in low resource regions like Jammu and Kashmir - India. Front Genet 11: 415.
7. Field MJ, Boat TF (2010) Rare diseases and orphan products: Accelerating research and development. Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development. Washington (DC): National Academies Press (US), Profile of Rare Diseases, USA.
8. Rodríguez BR, Sánchez GJC, Cortés MJ (2023) Pregnancy, childbirth, puerperium, breastfeeding, and sexuality in the world of rare diseases. Healthcare (Basel) 11(9): 1351.
9. Abozaid GM, Kerr K, McKnight A, Al-Omar HA (2022) Criteria to define rare diseases and orphan drugs: A systematic review protocol. BMJ Open 12(7): e062126.
10. Adachi T, El-Hattab AW, Jain R, Nogales CKA, Quirland LCI, et al. (2023) Enhancing equitable access to rare disease diagnosis and treatment around the world: A review of evidence, policies, and challenges. Int J Environ Res Public Health 20(6): 4732.
11. Hernandez LM, Blazer DG (2006) Genes, behavior, and the social environment: Moving beyond the nature/nurture debate. Institute of Medicine (US) committee on assessing interactions among social, behavioral and genetic factors in health. Washington (DC): National Academies Press (US), USA.
12. GUaRDIAN Consortium, Sivasubbu S, Scaria V (2019) Genomics of rare genetic diseases-experiences from India. Hum Genomics 14(1): 52.
13. Indian Council of Medical Research, Government of India. National Policy for Rare Diseases, 2021.
14. Might M, Crouse AB (2022) Why rare disease needs precision medicine-and precision medicine needs rare disease. Cell Rep Med 3(2): 100530.
15. Rinaldi A (2005) Adopting an orphan. EMBO Rep 6(6): 507-510.
16. Fernandez MA, Gouveia S, Couce ML (2018) NGS technologies as a turning point in rare disease research , diagnosis and treatment. Curr Med Chem 25(3): 404-432.

17. Vinkšel M, Writzl K, Maver A, Peterlin B (2021) Improving diagnostics of rare genetic diseases with NGS approaches. J Community Genet 12(2): 247-256.

18. Brittain HK, Scott R, Thomas E (2017) The rise of the genome and personalised medicine. Clin Med (Lond) 17(6): 545-551.

19. Larizza L, Cubellis MV (2023) Rare diseases: Implementation of molecular diagnosis, pathogenesis insights and precision medicine treatment. Int J Mol Sci 24(10): 9064.

20. Liu J, Barrett JS, Leonardi ET, Lee L, Roychoudhury S, Chen Y, et al. (2022) Natural history and real-world data in rare diseases: Applications, limitations, and future perspectives. J Clin Pharmacol 62 Suppl 2(Suppl 2): S38-S55.

21. Haq I, Brashear A (2023) The vital role of natural history studies in rare disease: insights from X-linked dystonia parkinsonism. Brain Commun 5(3): fcad125.

22. White F (2020) Application of disease etiology and natural history to prevention in primary health care: A discourse. Med Princ Pract 29(6): 501-513.

23. Papadimitriou S, Gazzo A, Versbraegen N, Nachtegael C, Aerts J, et al. (2019) Predicting disease-causing variant combinations. Proc Natl Acad Sci USA 116(24): 11878-11887.

24. Katelaris CH (2014) Rare diseases and expensive drugs. Asia Pac Allergy 4(2): 73-74.

25. Hughes DA, Poletti HJ (2016) Profitability and market value of orphan drug companies: A retrospective, propensity-matched case-control study. PLoS One 11(10): e0164681.

26. Davies EH, Fulton E, Brook D, Hughes DA (2017) Affordable orphan drugs: A role for not-for-profit organizations. Br J Clin Pharmacol 83(7): 1595-1601.

27. Ministry of Health and Family Welfare, Government of India. Initiatives by the Government for the treatment of rare diseases.

28. (2010) Understanding genetics: A district of Columbia guide for patients and health professionals. Genetic Alliance; District of Columbia Department of Health. Washington (DC): Genetic Alliance.

29. Loewe L, Hill WG (2010) The population genetics of mutations: Good, bad and indifferent. Philos Trans R Soc Lond B Biol Sci 365(1544): 1153-1167.

30. Jackson M, Marks L, May GHW, Wilson JB (2020) The genetic basis of disease. Essays Biochem 62(5): 643-723.

31. Duan D, Goemans N, Takeda S, Mercuri E, Aartsma RA (2021) Duchenne muscular dystrophy. Nat Rev Dis Primers 7(1): 13.

32. Venugopal V, Pavlakis S (2023) Duchenne muscular dystrophy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.

33. Darras BT, Urion DK, Ghosh PS (2022) Dystrophinopathies. In: Adam MP, Feldman J, Mirzaa GM, Roberta AP, Stephanie E W, Lora JHB, Karen WG, Anne A, (Eds.), GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle.

34. Martinez DB, Barrero MJ (2022) Epigenomic approaches for the diagnosis of rare diseases. Epigenomes 6(3): 21.

35. Fu MP, Merrill SM, Sharma M, Gibson WT, Turvey SE, et al. (2023) Rare diseases of epigenetic origin: Challenges and opportunities. Front Genet 14: 1113086.

36. Katsanis SH, Katsanis N (2013) Molecular genetic testing and the future of clinical genomics. Nat Rev Genet 14(6): 415-426.

37. Roberts AD, Wadhwa R (2023) Orphan drug approval laws. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.

38. Gabay M (2019) The orphan drug act: An appropriate approval pathway for treatments of rare diseases? Hosp Pharm 54(5): 283-284.

39. Augustine EF, Adams HR, Mink JW (2013) Clinical trials in rare disease: Challenges and opportunities. J Child Neurol 28(9): 1142-1150.

40. Logviss K, Krievins D, Purvina S (2018) Characteristics of clinical trials in rare vs. common diseases: A register-based Latvian study. PLoS One 13(4): e0194494.

41. Gammie T, Lu CY, Babar ZU (2015) Access to orphan drugs: A comprehensive review of legislations, regulations and policies in 35 countries. PLoS One 10(10): e0140002.

42. Herder M (2017) What is the purpose of the orphan drug act? PLoS Med 14(1): e1002191.

43. Kepplinger EE (2015) FDA's expedited approval mechanisms for new drug products. Biotechnol Law Rep 34(1): 15-37.

44. Gogtay NJ, Ravi R, Thatte UM (2017) Regulatory requirements for clinical trials in India: What academicians need to know. Indian J Anaesth 61(3): 192-199.

45. Bai JP, Barrett JS, Burckart GJ, Meibohm B, Sachs HC, et al. (2013) Strategic biomarkers for drug development in treating rare diseases and diseases in neonates and infants. AAPS J 15(2): 447-454.

46. Field MJ, Boat TF (2010) Rare diseases and orphan products: Accelerating research and development. Institute of Medicine (US) Committee on accelerating rare diseases research and orphan product development. Washington (DC): National Academies Press (US) Regulatory Framework for Drugs for Rare Diseases.

47. Moors EHM, Faber J (2007) Orphan drugs: Unmet societal need for non-profitable privately supplied new products. Res Policy 36(3): 336-354.

48. Litterman NK, Rhee M, Swinney DC, Ekins S (2014) Collaboration for rare disease drug discovery research. F1000Res 3: 261.

49. Hoffmann D, Haapasalo A (2022) Patient-derived skin fibroblasts as a model to study frontotemporal lobar degeneration. Neural Regen Res 17(12): 2669-2671.

50. Madelaire CB, Klink AC, Israelsen WJ, Hindle AG (2022) Fibroblasts as an experimental model system for the study of comparative physiology. Comp Biochem Physiol B Biochem Mol Biol 260: 110735.

51. Wang H, Yang Y, Liu J, Qian L (2021) Direct cell reprogramming: Approaches, mechanisms and progress. Nat Rev Mol Cell Biol 22(6): 410-424.

52. Hines TJ, Lutz C, Murray SA, Burgess RW (2022) An integrated approach to studying rare neuromuscular diseases using animal and human cell-based models. Front Cell Dev Biol 9: 801819.

53. Villalón GI, Álvarez CM, Suárez RJM, Povea CS, Talaverón RM, et al. (2020) Precision medicine in rare diseases. Diseases 8(4): 42.

54. Wang RC, Wang Z (2023) Precision medicine: Disease subtyping and tailored treatment. Cancers (Basel) 15(15): 3837.

55. Roth SC (2019) What is genomic medicine? J Med Libr Assoc 107(3): 442-448.

56. Patch C, Middleton A (2018) Genetic counselling in the era of genomic medicine. Br Med Bull 126(1): 27-36.

57. Crellin E, McClaren B, Nisselle A, Best S, Gaff C, et al. (2019) Preparing medical specialists to practice genomic medicine: Education an essential part of a broader strategy. Front Genet 10: 789.

58. Hamamy H (2012) Consanguineous marriages: Preconception consultation in primary health care settings. J Community Genet 3(3): 185-192.

59. Nascimento CRD, Basílio DDS, Lopes JM, Cansanção IF (2021) Analyzing inbreeding and estimating its related deficiencies in Northeastern Brazil. J Pediatr Genet 11(4): 272-278.

60. Hussein N, Henneman L, Kai J, Qureshi N (2021) Preconception risk assessment for thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease. Cochrane Database Syst Rev 10(10): CD010849.

61. Andrews LB, Fullarton JE, Holtzman NA (1994) Assessing genetic risks: Implications for health and social policy. Institute of Medicine (US) committee on assessing genetic risks. Washington (DC): National Academies Press (US), Social, Legal, and Ethical Implications of Genetic Testing.

62. Hershberger PE, Gallo AM, Kavanaugh K, Olshansky E, Schwartz A, et al. (2012) The decision-making process of genetically at-risk couples considering preimplantation genetic diagnosis: Initial findings from a grounded theory study. Soc Sci Med 74(10): 1536-1543.

63. Read AP, Donnai D (2012) What can be offered to couples at (possibly) increased genetic risk? J Community Genet 3(3): 167-174.