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Refocusing on Rare Diseases

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The US Food and Drug Administration (FDA) approval in December 2023, of two milestone treatments, Casgevy and Lyfgenia, representing the first cell-based gene therapies for the treatment of a rare disease called sickle cell disease (SCD) in patients 12 years and older, is a huge development. With rare diseases posing significant challenges due to the scarcity of information, limited research, and insufficient awareness among healthcare professionals and the public, introduction and approval of specific treatments can provide a much needed boost to tackle the growing burden of rare diseases globally. However, an integrated approach with enhanced coordination and cooperation across the ecosystem is the need of the hour.

The scientific community has a critical role to play in accelerating rare disease research and contributing to improving diagnosis and treatment. Although innovations in sequencing technology and machine learning approaches are positively affecting diagnostic success, more coordinated efforts are needed to move towards effective therapies for this important, and underestimated, class of diseases, which is not so rare any longer.

In November 2023, the Union Health Ministry authorised the sale of four generic medications for the treatment of rare diseases. This approval is a significant milestone in the fight against rare diseases in India. These approved indigenous products, along with other products yet to be approved, will aid patients suffering from rare diseases by improving quality of life as well as overall healthcare outcomes. However, a major obstacle to effectively combating rare diseases in India is the lack of awareness and inadequate diagnosis in the country, says GlobalData, a leading data and analytics company.

The four approved medications are used to treat Wilson's disease, Gaucher's disease, Tyrosinemia Type I and Dravet-Lennox Gastaut syndrome. Earlier, these therapies were imported to India and would cost Rs 1.8- 3.6 crore for annual treatment. With this approval, patients with rare diseases can now access these therapies at a significantly reduced cost of Rs 3- 6 lakh, which is 100 times less than the imported therapies. Over the next few months, the ministry is expected to release medications for additional rare illnesses, such as hyperammonaemia and phenylketonuria.

Furthermore, in December 2023, the US Food and Drug Administration (FDA) announced the approval of first gene therapies to treat patients with Sickle Cell Disease, a rare, debilitating and life-threatening blood disorder with significant unmet need.

The new technical advances in rare disease genetics research that apply the latest technologies to improve diagnosis ensures an exciting time ahead but a lot more needs to be done. The rare disease research is currently very siloed and often organised around single disorders. A more integrated structure with appropriate support for researchers to coordinate across rare diseases is required to minimise redundant efforts, increase efficiency, potentially accelerate development and the

implementation of successful therapies in India and around the world.

Challenges surrounding Research & Innovation for Genetic Diseases

The estimated burden of rare genetic diseases is 72- 96 million in India and the average time for diagnosis is 7 years. No effective treatment is available for many of the disorders and less than 5 per cent have therapies. Thus, the right diagnosis and treatment are crucial for improving the quality of the life of patients.

Quoting an example, **Dr Jogin Desai, Chief Executive Office, Eyestem Research** says, “Retinitis pigmentosa is a rare congenital retinal disease which is significantly underdiagnosed due to lack of awareness leading to insufficient data and thus societal inaction. We need to integrate genetic insights into societal knowledge, and lay the groundwork for a comprehensive understanding of these often-overlooked conditions.”

From the diagnostic perspective, the optical genome mapping test is garnering attention as a highly advanced diagnostic tool that uses cutting-edge technology to provide a comprehensive and accurate assessment of genetic changes in patients. Optical genome mapping can be used for accurate diagnosis where more common or traditional techniques fail.

Explaining the clinical utility of optical genome mapping, **Dr Karthik Bharadwaj, Scientist, Genetic disorders- Diagnostics, CSIR- Centre for Cellular & Molecular Biology (CCMB)** says, “Optical Genome Mapping is automated and performs with more than 95 per cent sensitivity. In a case of Hemophilia A where whole exome sequencing was not able to report a common mutation, optical genome mapping has helped in identifying inversion in intron 22. In another case with developmental delay, dysmorphism, a balanced translocation was identified in chromosome 12 showing ~16mb, fusion depicting copy number gain. Other examples include fragile X and disruption of *AUTS2* gene. However, the limitations with optical genome mapping include lack of adequate reference data, inability to detect structural variants across acrocentric regions and poorly labelled regions.”

On the other hand, big pharma companies, by virtue of their resources and influence, are making efforts in developing new drugs and therapies for rare diseases in India, but there are multiple challenges that lie ahead of them.

Because of the low number of affected populations with rare genetic diseases, they have been recognised in the Orphan Drug Act 1983 which is formulated for drugs with a limited market. With the narrow market, drug manufacturers need some incentives to invest in this cause. Therefore, the government needs to formulate certain laws to boost the production of these drugs indigenously.

Another possible challenge that can come across in developing therapies is in the form of market challenges or small population sizes. Even after developing therapies, the challenge of the market comes with high costs and with the idea of developing drugs for a small population, thus the industry interference is limited. This can be tackled by introducing smart acceleratory pathways from government funding and certain waivers for clinical trials. There is a need to look through a global perspective, and the stringent rules that hinder pharmaceutical companies from looking into rare diseases.

According to **Dr Rita Sarin, Advisor, Intellectual Property**, “We cannot overlook the financial hurdles hindering drug development for rare diseases. The lengthy, expensive process of creating a drug molecule is a major deterrent for pharmaceutical companies due to low returns. Further, there are intricacies of licensing and patenting. To ensure success in indigenous medication development, collaborative research should be fostered by integrating research pipelines, paving the way for industry-academia to drive innovations.”

Adding his perspective, **Dr Ashwin Dalal, Head, Diagnostics Division, Centre for DNA Fingerprinting and Diagnostics** , highlights “India's substantial contribution to the rare genetic disease burden is due to its vast population and diversity. There is absence of a specific rare disease definition due to inadequate epidemiological data. Traditional diagnostics have shifted from cytogenetics to next generation sequencing (NGS), yet treatment cost remains a challenge. For determining disease prevalence and carrier frequency, technologies like exome sequencing can be used. Also, there are various country-level initiatives like India's Rare Disease Policy under which 12 centres of excellence (CoEs) have been established across the country . The National Policy for Rare Diseases categorises rare genetic diseases into three groups, granting eligible patients financial aid and offering up to Rs 50 lakh for select patients but that remains a temporary solution.”

Laying focus on the CoEs, these are tertiary care multi-speciality centres which come with their own set of challenges. The first challenge is to sensitise the medical staff for the rare diseases, who otherwise receive patients with multiple medical manifestations. Due to heterogeneity of the conditions of the rare disease patients, it is difficult to tell the exact number of rare disease patients visiting the centres. Also in such conditions, the patients need to visit multiple wards and it is thus time consuming and difficult for the patients as well as the clinicians. The procurement of the medicines, the associated

paperwork, delays in receiving the drugs and the changes in the required dosage of the medicines that are weight dependent, are other associated challenges.

What's the right approach?

With the democratisation of knowledge after COVID-19, it is easier to create awareness of therapeutics and discovery of potential drugs for rare disease. If more companies in India are established to tackle drug discovery, there will be an increase in treatment, i.e. the treatment would not be rare and hence the costs will be brought down gradually. But how do we translate this in the form of a permanent solution?

"A few success stories are all that are needed for a model to go forward. We need to make prenatal and newborn screening mandatory for treatable disorders. Exploring repurposed and low-cost drugs is required, establishing infrastructure for drug testing, and fostering collaboration partnerships between government, administrative and private stakeholders - both in R&D and policy is required. Building strong partnerships between researchers, clinicians, and industry stakeholders; utilising cutting edge technologies such as CRISPR and mRNA technologies to bring down costs and ensure quality manufacturing; exploring philanthropic funding, CSR initiatives, and the National Research Foundation; and creating a federation of databases and leveraging digital tools for virtual consultations are some of the key strategies to be implemented", says **Dr Rakesh Mishra, Director, Tata Institute for Genetics and Society (TIGS) India.**

A crucial observation underscores the potential of government laboratories to motivate private companies to engage in the development of therapeutics for rare genetic diseases. The need to address awareness of these diseases among people can be a milestone in dealing with respite care and disease management apart from therapeutics and diagnostics.

"Early diagnosis; epidemiological data collection; therapeutics availability and affordability; awareness and expertise development; and dedicated research initiative are some of the various ways in which the government is supporting rare genetic disease research. To address the critical challenges of therapeutic availability and affordability, there should be an increase in the number of grants, more collaboration, and networking efforts", says **Dr Nabendu Chatterjee, Biochemist, ICMR-National Institute of Cholera and Enteric diseases.**

He further advocates for existing government initiatives such as genomics projects, networking between patient advocacy groups and other stakeholders, therapeutics development for inherited rare diseases, and the National Apex Committee: National Consortium for Research and Development on Therapeutics in Rare Diseases (NCRDTRD).

The need for policy reforms, ensuring easier access to healthcare and research opportunities for patients, is resonating across the ecosystem. It all requires integration in order to set in motion the pathways to accelerate solutions in the rare genetic diseases field.

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(Key takeaways of this article are based on the inputs provided by various experts at the Rare Genetic Diseases Research Summit (REDRESS) 2023 hosted by the Tata Institute for Genetics and Society (TIGS) and the Organization for Rare Diseases India (ORDI), along with the Indian Council for Medical Research (ICMR) as the knowledge partner, with BioSpectrum as the media partner)