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Challenges in Diagnosing Rare Movement Disorders: From Clinical Clues to Genomic Testing

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ABSTRACT

One of the largest problems in contemporary medicine is still rare diseases, which afflict less than 200,000 people in the United States or less than 1 in 2,000 in Europe. Healthcare systems and pharmaceutical firms have long ignored these illnesses since so few persons are affected. By providing incentives that spurred businesses to seek cures for these underappreciated illnesses, the Orphan Drug Act of 1983 represented a turning point. Since then, there has been a significant increase in interest in the development of orphan drugs, particularly since some medicines have shown both commercial and medical value. The field is changing as a result of recent scientific discoveries. Artificial intelligence, next- generation sequencing, and personalised medicine are examples of technologies that are making it easier than ever for researchers to comprehend rare diseases and provide tailored treatments. Advances in drug repurposing, gene therapy, and cell-based therapies are providing hope for diseases that were previously thought to be incurable. Although there are still issues with diagnosis, access, and long-term finance, development has also been hastened by international partnerships and changing regulatory frameworks. The market for orphan drugs is still growing worldwide, which is a result of both scientific advancement and growing awareness of unmet patient needs. To advance therapeutic options for communities with rare diseases, it will be essential to fortify alliances, enhance patient registries, and align global incentives.

Keywords: orphan drug; rare diseases; Orphan Drug ACTION; orphan Diseases.

Introduction

Rare diseases are significantly more frequent than most people realise, affecting about 10% of individuals globally as of 2024.[1,2] Because there are few treatments and little information available, rare diseases have a significant impact on healthcare worldwide. With only 5% of rare diseases having an approved treatment, patients are still underserved despite increased attention being paid to the development of orphan drugs.[3] Rare diseases are challenging to manage for a variety of reasons. A illness is deemed rare by the World Health Organisation if it affects less than 6.5 to 10 individuals out of every 10,000.[4] The burden of rare diseases varies by area and has a substantial worldwide influence. They impact over 25 million people in North America alone.[5] Roughly 6% of people in Europe suffer from uncommon diseases.[6] These figures add to the assumption that 350 million people globally suffer from uncommon diseases.[7] In a similar vein, Table 1 lists a number of uncommon illnesses that have significantly improved our knowledge of human genetics and molecular treatments. Treatments for more prevalent ailments such essential hypertension, coronary artery disease, and some types of cancer have also been made possible by these findings.[8,9]

Definitions

Orphan diseases were defined in 1983 by the Orphan treatment Act (ODA) as illnesses that are so uncommon in the US that a firm could not reasonably expect to repay the cost of developing a treatment for them through U.S. sales alone. The statute gave hemin and diaziquone the first official orphan drug designations in the same year.[10] It describes illnesses that affect fewer than 200,000 Americans and for which it is improbable that a business could recoup the expenses of creating and marketing a medication for that ailment through sales in the United States alone.[11] The number of persons affected with rare diseases varies by country; in the EU, it is less than 5 in 10,000, in Japan it is less than 50,000, in Australia it is less than 2,000, and in the WHO it Is between 0.65 and 1 per 1,000.[12,13]

GLOBAL INITIATIVES IN ORPHAN DRUG DE-VELOPMENT

1. Acts and Legislation

Updating health rules and offering legislative incentives that promote the discovery and development of remedies for certain ailments are more effective ways to combat rare diseases.

USA :

Treatments for rare diseases have advanced thanks in large part to incentives including market exclusivity, financial support, fee waivers, tax credits, protocol guidance, and quicker approval procedures.[14]

There were just ten authorised medications for uncommon disorders prior to the Orphan Drug Act of 1983. To promote the creation of novel treatments, the Act included financial incentives, research grants, tax credits, fee exemptions, priority reviews, and market exclusivity.[15]

Europe :

Orphan drug legislation, which provide 6–10 years of market exclusivity and fee waivers up to £100,000, were implemented by the EU. A patient registry was established by EMA's

COMP in 2015 to facilitate post-approval safety and efficacy research.[16] The European Joint Programme on Rare Diseases and the European Clinical Research Infrastructure

Network both concentrate on expanding research and enhancing therapies for uncommon diseases.[17]

Germany

The goal of Germany's new national project, CORD-MI, is to improve data sharing and documentation on rare diseases across German university hospitals and research facilities.[18]

Canada

The Canadian Health Authority defines rare diseases as dangerous, frequently fatal, or chronic ailments that only afflict a small percentage of persons.[19] In order to create a comprehensive national policy, the Canadian Health Authority conducted an online survey in 2021 to get Canadians' opinions on treatments for uncommon diseases.[19]

China

During a meeting in 2010 to define rare diseases, the Chinese government proposed that a condition be classified as rare if its incidence in newborns is less than 1 in 10,000 or if it affects fewer than 1 in 500,000 adults.[20] The New Drug Approval Regulation (1999), Drug Registration Regulation (2007), and Approval Procedures for Drug Registration (2009) are important rules established by the State Food and Drug Administration to expedite the registration and approval of orphan medications.[20] China has created its own official classification system, although it does not have a specific definition for uncommon diseases.[21]

Artificial Intelligence and Machine Learning

AI has the potential to improve prognosis, diagnosis, and treatment.[22] A kind of artificial intelligence called machine learning makes predictions using data. Drug research for uncommon disorders including ALS, JPLS, and hereditary spastic paralysis is aided by tools like AlphaFold, which simulate proteins like Alsin.[23] Cutting-edge techniques are being applied in contemporary clinical trials to improve the accuracy and efficiency of research. Particularly when working with small patient populations, artificial intelligence and machine learning algorithms aid in trial design. In the meanwhile, pharmacokinetic

simulations and computational models enable researchers to forecast potential

medication interactions and identify optimal dosage approaches.[24] Future cures for rare diseases like neuronal ceroid lipofuscinoses will be driven by improved clinical trial designs, more robust infrastructure and knowledge, and more intelligent strategies to prioritise research.[25]

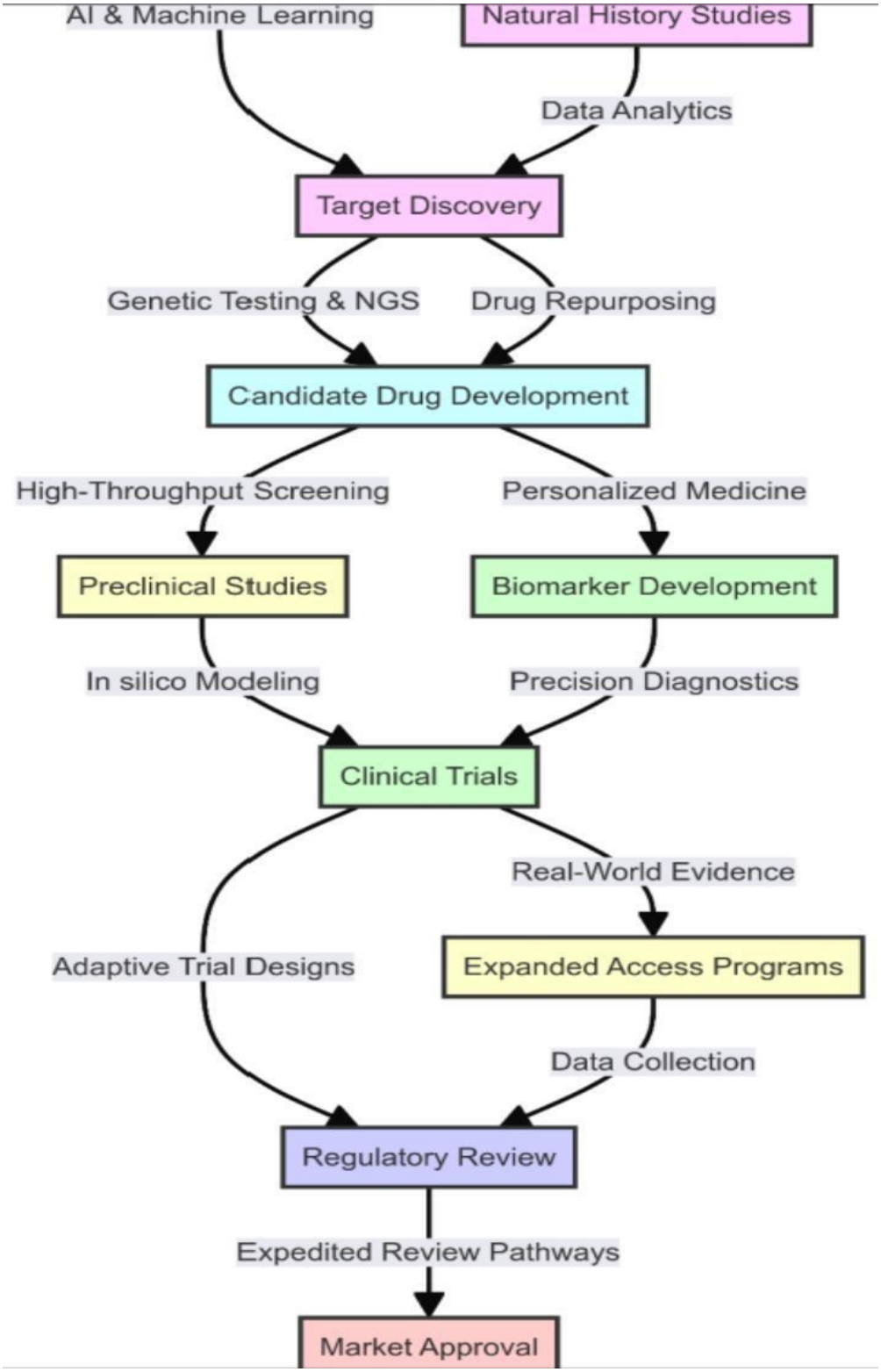

Fig.1: Key technological and therapeutic advancements in orphan drug development. (A higher resolution / colour version of this figure is available in the electronic copy of the article)

Therapeutic Approaches:

Cellular Therapy

Orphan biological agents make up about 40% of all approved biological agents.[15] For rare illnesses, a number of gene treatments are now approved. Luxturna, Zolgensma, Kymriah, Yescarta, Breyanzi, Abecma, Roctavian, and Zynteglo in the US; Strimvelis, Luxturna, Zynteglo, and Libmeldy in the EU. The first ex-vivo stem cell treatment for ADA-SCID to receive EMA approval is called Strimvelis.[26]

Protein Replacement Therapy

Rare disorders brought on by protein deficiencies are treated with protein replacement therapy. Factor VIII and IX for haemophilia A and B are two examples. From plasma-derived proteins to modified recombinant proteins and more recent treatments like emicizumab, the field has changed.[27]

Enzyme Replacement Therapy

Lysosomal storage diseases including Pompe's and Gaucher's disease are treated with enzyme replacement therapy (ERT). ERTs have been giving patients frequent enzyme injections for the duration of their lives since the 1990s. The first illness to be treated in this manner with glucocerebrosidase extracted from human placentas was Gaucher's disease.[28]

Table.1: List of commercial drivers for the success of drug development for orphan diseases[29]

Commercial Drivers for Orphan Drug Development

1. Government incentives, such as grants, tax credits, and waived application fees
2. Clinical trials are small and tracked quickly.
3. greater success with regulations compared to non-orphan medications
4. High-end medication costs
5. Reduced obstacles to approval
6. Reduced spending on marketing
7. Exclusivity of orphan drugs
8. Multiple approvals for orphan diseases

Table.2: Incentives provided to the manufacturer of orphan drugs under the oda[30,31] Orphan Drug Act:Incentive to Drug Manufacturer

Tax Credit: Up to half of the costs associated with clinical research may be reimbursed to sponsors.

Exclusivity: An orphan product has seven years of exclusive marketing rights after approval.

Waiver of Prescription Drug User Fees: When filing a marketing application to the FDA, the sponsor is exempt from paying the costs typically mandated under the Prescription Drug User Fee Act.

Annual Grants: An annual grant programme is in place to pay for approved clinical testing expenses. Sponsors may get up to $200,000 annually for up to three years in Phase I clinical trials.

CONCLUSION :

Rare movement disorders are difficult to diagnose and sometimes have mild or overlapping clinical characteristics. Combining genetic testing with thorough clinical examination improves diagnostic accuracy and guides focused treatment. In order to enhance patient outcomes, decrease diagnostic delays, and increase comprehension, interdisciplinary cooperation and ongoing research are essential.

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