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The Role of Precision Medicine in Rare Diseases

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ABSTRACT

Precision medicine, driven by advances in next-generation sequencing (NGS) and genomics, is transforming the diagnosis and treatment of rare diseases. Rare diseases, often genetic, present unique challenges due to their low prevalence and the heterogeneity of symptoms. Precision medicine offers a promising solution by channeling therapies to an individual's genetic profile, providing earlier diagnoses, and guiding treatment decisions. This review discusses the definition and prevalence of rare diseases, explores the challenges in their diagnosis and treatment, and highlights the potential of precision medicine through case studies and emerging technologies. Future directions include overcoming data integration challenges and fostering collaborations in bioinformatics and AI for improved therapeutic outcomes.

Keywords: Precision Medicine, Rare Diseases, Next-Generation Sequencing (NGS), Genomics, Personalized Therapy.

INTRODUCTION

The remarkable advances in the understanding of the human genome and the completion of the Human Genome Project have fostered hopes for more efficient and less costly early diagnosis of common, rare, and undiagnosed diseases, as well as the discovery of new drug targets and biological insights into drug action. To track molecular genetic variation on a grand scale, biomolecules have to be analyzed. Therefore, next-generation sequencing currently uses whole genome sequencing and whole exome sequencing technologies. Since guidelines recommend a broad NGS-based approach for rare diseases, developing pre-analytical components is necessary, from sample collection to sequencing analyses, interpretation, and reporting. Various bioinformatics approaches are deployed to extract genetic information from heterogeneous raw data and translate it to clinical use, recalling the importance of strict standard operating procedures and transparent protocols [1, 2]. Owing to the extraordinary capability of high-throughput next-generation sequencing techniques to generate astounding volumes of genomic data from multiple individuals in parallel, the recognition of genetic variants associated with human diseases has been significantly accelerated. The affluence of human genetic variants detected by NGS, including common ones segregating in human populations and very rare ones, whose carriers have the diseases, is exponentially increasing. Exome sequencing, which sequences most of the protein-coding regions of the genome, provides an acceptable cost-performance ratio for the identification of rare variants in a multitude of coding genes. These advances in the characterization of genetic variation in the human genome have paved the way for the current era of precision medicine. On an individual basis, an increasing number of therapeutic and preventive applications aim at matching the most appropriate medical care with individual molecular and genetic criteria. More recently, these scientific advances have engendered hopes for a different approach to the detection of rare, non-familial diseases, provided that the patient's genomic data are available [3].

UNDERSTANDING RARE DISEASES

Rare diseases, also known as orphan diseases, are conditions that affect a small percentage of the population. A disease is classified as rare when it affects fewer than 200,000 patients. Diseases are considered rare when less than 1 in 2,000 patients are affected, and a disease is rare when it affects less than 50,000 patients. Despite their relative rarity, rare diseases are not uncommon; there are more than 7,000 known rare diseases worldwide. These diseases combine to affect 25–30 million people in the United States and 30 million people in the European Union. Many rare diseases fall under the category of genetic diseases, which are caused by alterations in the DNA sequence. Approximately 80% of rare diseases are of genetic origin, with 72% of rare diseases due to a single gene mutation and 9% due to chromosomal aberrations. Importantly, 70% of rare diseases appear in childhood, and 30% of affected children do not survive beyond 5 years of age. Nevertheless, there is hope for patients and families affected by rare diseases, as the field of precision medicine is emerging [4, 5]. Rare diseases present challenges for diagnosis and treatment. The diagnosis process is often lengthy, with patients consulting numerous healthcare professionals and undergoing multiple tests. This delay can allow the disease to progress, potentially becoming irreversible or degenerative. Some rare diseases, such as Duchenne muscular dystrophy and Becker muscular dystrophy, can lead to significant symptoms like loss of mobility and cardiac complications. Unfortunately, many rare diseases lack reliable markers for diagnosis. Additionally, early treatment is crucial for certain rare diseases, like lysosomal storage disorders. Misdiagnosis is common, with patients often being misdiagnosed with similar conditions. Neuropsychiatric symptoms are often associated with rare diseases, and determining whether they are psychiatric in nature can be challenging. Funding gaps exist, particularly in preclinical animal modeling for diseases with subtle symptoms [6].

DEFINITION AND PREVALENCE

Rare diseases, also known as orphan diseases, affect a limited fraction of the population, approximately 1 in 2000 individuals. These diseases receive less research and resources due to their limited patient population, resulting in a limited number of drugs available. Globally, there is a 7.1 percent chance of being diagnosed with a rare disease in one's lifetime. A catalog has identified 6,898 rare diseases, with 678 recorded in the population group of one thousand to ten thousand patients. These diseases can be genetic, caused by infections, or environmental factors. Although rare diseases make up only 1% of the total population of diseases, they represent a paradoxical majority due to their diversity. Over 70% of rare diseases are considered orphan diseases, with few treatment options available. In the US, an estimated 95% of these diseases remain untreated [7].

CHALLENGES IN DIAGNOSIS AND TREATMENT

The field of rare diseases presents formidable challenges in diagnosis and treatment. These are conditions that affect fewer than 200,000 people in the United States, or fewer than five in 10,000 people in the European Union. The rarity of these disorders leads to a dearth of funding, resulting in only six percent having a treatment in the United States and fewer than two in the European Union. Inherited metabolic diseases, storage diseases, and genetic syndromes are rarely studied, leaving thousands of patients without hope or understanding of their ailment. Although there has been an explosion of genetic information, current regulations do not provide adequate incentives for companies to develop treatments. As a result, hopes are placed on publicly funded entities. 8 A lack of proper accounts of nationality and race in the study of diseases can lead to over- and under-diagnoses in particular groups. For instance, with metabolic diseases such as sickle cell anemia and cystic fibrosis that are common among certain nationalities, those outside of these groups might fall through the cracks. In July 2000, the United States Congress took action by passing the Rare Disease Act of 2000, which stated that a Committee on Rare Diseases should be established to improve education and training for health care professionals, patients and families, and public health officials regarding rare diseases. In Europe, in July 2000, the Orphan Drug Regulation was legislated that provided companies with a ten-year period of market exclusivity if a treatment could be provided. Additionally, the Office of Rare Diseases in the National Institutes of Health was created to increase funding for research on rare diseases [9].

PRECISION MEDICINE: CONCEPTS AND APPLICATIONS

The term "precision medicine" refers to classifying diseases based on omics-based analyses. It also involves individualized treatment using genetic and non-genetic data. Precision medicine focuses on the disorder rather than the individual patient. It involves complex treatments based on multiple inputs and aligns with healthcare's goals of predicting outcomes, reducing side effects, and lowering costs. Omics technologies, big data, AI, digital/mobile/telemedicine, and IoT are used. Spatial/temporal and geospatial data can also be incorporated into the models [10, 11]. Omics-based classification of complex diseases, including rare diseases, is a key application of precision medicine. Efforts to develop technologies like single-cell long-read sequencing and computational algorithms for systems genomics are ongoing. However, there are omics-agnostic propositions for precision medicine, including cohort-wide approaches that rely on text-based or imaging data. Features such as metabolic phenotypes, gut microbiome profiling, and shared genetic background are used to promote dietary interventions. While systemic factors are important, individual genetic information remains a significant factor in outcomes. Exome sequencing has been used to search for rare diseases, confirming the presence of a pathogenic mutation [12].

CASE STUDIES OF PRECISION MEDICINE IN RARE DISEASES

Precision medicine has made strides in rare diseases, translating genotypic and phenotypic variations into effective treatment. Case studies of successful initiatives in Laron syndrome show improved clinical outcomes. A clinical trial of a dual agonist resulted in weight gain, lean mass increase, and reduced fat and glucose levels. Chronic granulomatous disease has also been a model for precision medicine. Genomic profiling can be used to discover drugs for rare diseases. Monogenic rare disease genes have been found to be risk genes for common diseases. Rare variants can provide insights into common diseases, and joint-variant analysis of genetic data is valuable. Prevalence benefits and secondary outcomes can help prioritize rare disease variants for investigation [13, 14].

CHALLENGES AND FUTURE DIRECTIONS

Despite the rapid advancements and successes of precision medicine in the field of rare diseases, several challenges remain before proposed models can be fully realized and implemented. A key consideration in the pursuit of personalized therapy is the large quantity of clinical and omic data generated, often from computational resources that can differ significantly in network architecture, processing and filtering approaches, or presented biological feedback, leading to inevitable differences in results and data interpretation and causing the challenge of data integration [15, 16]. The replacement of the "one-size-fits-all" therapeutic model with targeted, personalized approaches requires a better understanding of pathophysiological mechanisms and the use of bioinformatics pipelines to transform big data into coherent formats. Collaborations are needed to establish common data formats and benchmarks for precision medicine and multi-omics approaches to rare diseases. Integrative AI/biosystem approaches can help expedite this process. Collaborations with technology partners specializing in deep bioinformatics will be required for laboratories focusing on rare diseases to utilize big data analyses and establish tailor-suited therapies for individual patients [17, 18].

CONCLUSION

Precision medicine offers a revolutionary approach to diagnosing and treating rare diseases by leveraging genetic and molecular data. Its ability to customize therapies based on individual genetic profiles can lead to earlier and more accurate diagnoses, personalized treatments, and better clinical outcomes. Despite the challenges of integrating vast amounts of genomic data and developing targeted treatments, advances in bioinformatics and technology continue to pave the way for precision medicine. Collaboration between healthcare providers, researchers, and technology partners is crucial to fully realize the potential of precision medicine, offering hope to millions of patients affected by rare diseases worldwide.

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